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THE A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system and to disseminate knowledge in this department of medicine.

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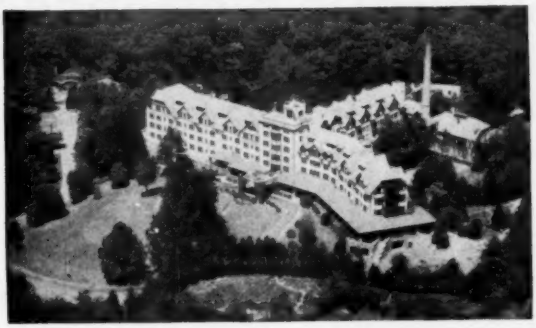

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BRAIN LESIONS ASSOCIATED WITH PROLONGED UNCONSCIOUSNESS

J. D. FRENCH, M.D.
LONG BEACH, CALIF.

IN RECENT years a large amount of data has accumulated concerning the function of the central cephalic portion of the brain stem in animals, an area about which little had previously been known. This information stems from the work of Magoun and his associates, who pointed out that the cephalic tegmentum, subthalamus and hypothalamus, and the medial portion of the thalamus function as an "activating system," excitation of which resulted in desynchronization of electrocortical activity and behavioral arousal of a sleeping animal. Supporting the contention that this area had importance in the complex arousal mechanism were the observations of Lindsley and associates [1] on the cat. They showed that electrolytic lesions strategically placed to destroy a portion of the region resulted in animals which were, among other things, chronically unresponsive to normally arousing stimuli and which continuously displayed a synchronous electroencephalographic tracing characteristic of stupor. Similar lesions in monkeys [2] produced even more devastating changes in their behavioral appearance, rendering them completely helpless and inert and reducing them to a state characterized by total loss of reactive adaptiveness, closely simulating the comatose human being.

Many observations have been recorded concerning the effect of vascular and traumatic disturbances in the cephalic portion of the brain stem in man, in almost all of which emphasis was placed on the profoundly depressed ability of the subject to react adaptively to his surroundings. The terms "coma," "stupor," and "unconsciousness" were used most frequently to describe this state, in which patients not only were incapable of reacting to their surroundings, but also lacked completely the ability to perform nutritive, protective, and restorative functions necessary for their survival. For this reason, undoubtedly, practically all such reports concern short-

From the Neurosurgical Section, Veterans Administration Hospital, Long Beach, Calif., and the Department of Surgery, University of California School of Medicine at Los Angeles.

Dr. H. W. Magoun participated liberally in the preparation of this report. Wilma Weeks, Timothy Dodge, Thomas Masterson, and Charles Bridgeman prepared the microscopic sections and the figures.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Lindsley, D. B.; Schreiner, L. H.; Knowles, W. B., and Magoun, H. W.: Behavioral and EEG Changes Following Chronic Brain Stem Lesions in the Cat, Electroencephalog. & Clin. Neurophysiol. **2**:483-498 (Nov.) 1950.

2. French, J. D., and Magoun, H. W.: Effects of Chronic Lesions in the Central Cephalic Brain Stem of Monkeys, A. M. A. Arch. Neurol. & Psychiat. **68**:591-604 (Nov.) 1952.

term observations, the patients so afflicted rarely surviving more than a few days, or, at most, two or three weeks. Analysis of the short-term clinical manifestations resulting from such lesions is difficult and unsatisfactory because neighborhood, and even remote, alterations in cerebral function are difficult or impossible to assess. Furthermore, it is quite possible that many of the clinical manifestations displayed are agonal, and not to be imputed directly to the brain-stem lesion. Evaluation of the behavior of patients with evidence of lesions in the cephalic portion of the brain stem of longer standing is somewhat more satisfactory. Here, not only is it surer that the clinical alterations are permanent, although compatible with survival of the patients, but it is more likely that lesions in the brain associated with these changes will be apparent in their entirety.

For these reasons, the available clinical material was examined for three patients with significant injury to the cephalic portion of the brain stem who survived six, seven, and nine months respectively. Two additional patients are described who appeared clinically very similar to the patients with brain-stem injury but whose lesions were found to be located elsewhere.

Analysis of the material on these patients and comparison with animal observations make it possible to extend information concerning the central cephalic portion of the brain stem. At least the appearance of patients afflicted with lesions in this area closely approximates in many respects that produced in animals by destruction of the reticular activating system. This similarity of behavioral appearance would seem to justify further evaluation of the area in animals as a means of expanding knowledge concerning its function in man.

REPORT OF CASES

Case 1.—F. T., a man aged 49, was admitted to the Veterans Administration Hospital Nov. 28, 1948, having been found unconscious on his doorstep. The next morning he was quite rational, and neurological examination revealed no abnormality. He had a series of convulsions, however, during the next two days, coincident with which it was found that he had grossly bloody spinal fluid. His convalescence was subsequently fairly normal, no physical abnormalities being apparent aside from rather pronounced hypertension. The blood gradually disappeared from the spinal fluid, but the pressure remained minimally elevated. As he was asymptomatic, however, it was decided to follow him in the outpatient department.

He reentered the hospital on Sept. 12, 1950, again comatose and with a scalp laceration, the suggestion being that he had fallen during a seizure. Complete hemiparesis of the right side, together with gross blood in the spinal fluid, led to an exploration of the left temporal region, during which laceration of that structure and a large subdural hematoma were found.

His subsequent course was characterized by essentially complete akinesis and coma. After an initial period of three weeks, during which he appeared to be moribund, he reached a state in which he would open his eyes and stare aimlessly for short periods during the day but would never attend or react adaptively to any stimulus whatever. He remained in this condition for the rest of his six-month survival period, requiring complete nursing care, including intragastric feeding. Repeated electroencephalographic recordings showed a stupor tracing which could not be desynchronized or altered in any way by normally arousing or painful stimuli (Fig. 1).

Examination of the Brain.—The anteroinferior two-thirds of the left hemisphere was essentially replaced by a hugely dilated left ventricle. Moderate dilatation was also present in the right ventricle; yet externally and on frontal sectioning the right hemisphere, together with the mediodorsal and posterior surfaces of the left hemisphere, appeared essentially normal. The iter and the fourth ventricle were also dilated. Major areas of destruction were present in the cephalic portion of the brain stem, the extent of these being determined by serially

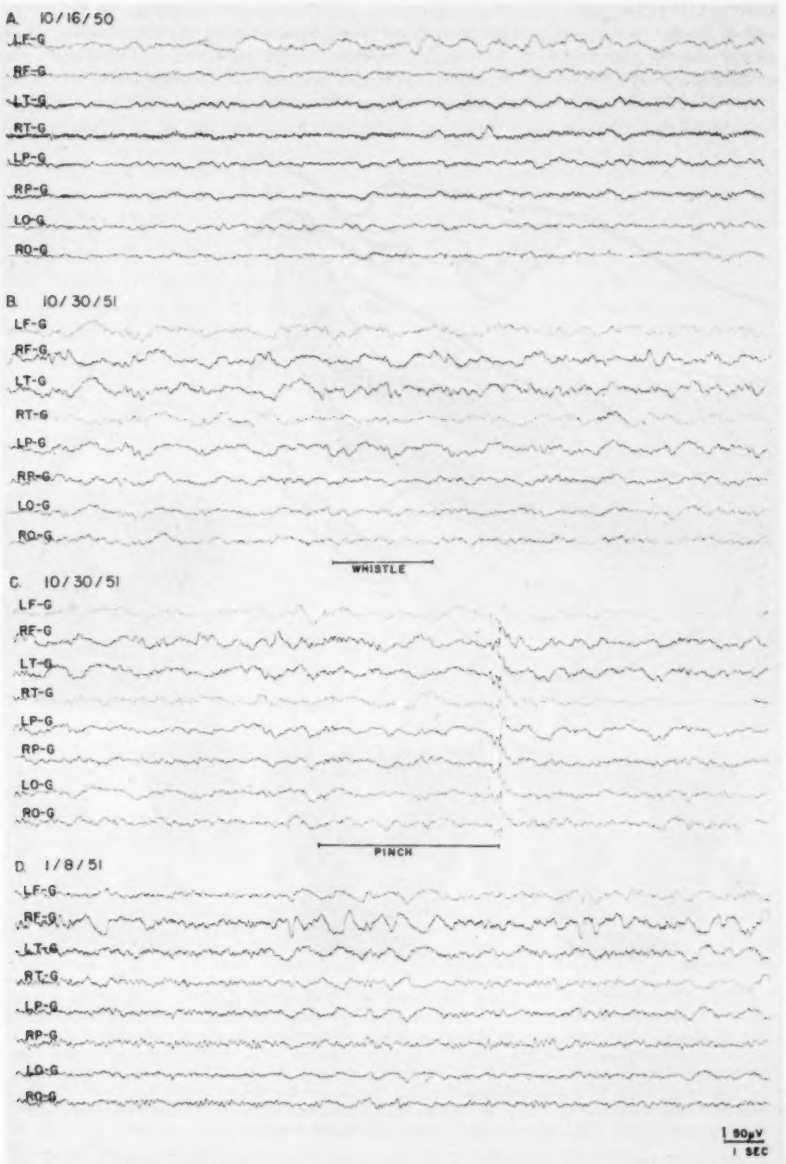

Fig. 1 (Case 1).—Monopolar electroencephalographic tracings taken at various times on Patient F. T., who was stuporous for approximately six months, are characterized by the presence of high-voltage slow activity which could not be desynchronized by afferent stimuli (*B* and *C*).

sectioning this structure. The most conspicuous disturbances were softenings in the basilar part of the pons and the tegmentum, with an additional focal softening in each mamillary body. Similar changes were seen in parts of the left thalamus, and the remainder of this structure was atrophied. Around many of these softened areas glial response was frequently abundant, while around others such a response was notably lacking. The regional lesion in the left side of the brain stem had destroyed a major portion of the internal capsule and part of the globus pallidus.

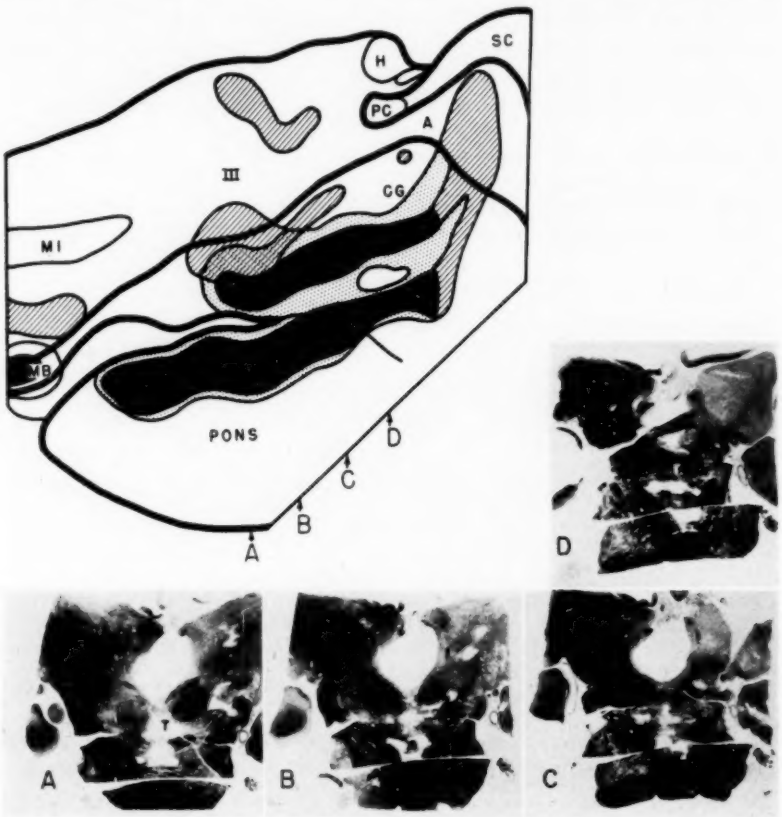

Fig. 2.—The diagram in the upper left corner is a midsagittal reconstruction of the serially sectioned brain stem of Patient F. T. Midline areas showing softening (black) and surrounding areas of gliosis (dots) are seen to occupy a major portion of the dorsal portion of the pons and the cephalic portion of the tegmentum. Laterally situated areas of destruction are cross-lined. Photographs of cross sections *A* to *D* (Weil stains), taken at designated levels on the reconstruction, show the extent of tegmental injury (*T*). The following abbreviations are used: *A*, aqueduct; *CG*, central gray matter; *H*, habenula; *MB*, mamillary body; *MI*, massa intermedia; *PC*, posterior commissure; *SC*, superior colliculus; *III*, third ventricle.

On the right side, the basal ganglia, internal capsule, thalamus, and subthalamus were, by comparison, minimally involved. Also, in contrast, the cortex of the right hemisphere, as well as the medial, dorsal, and posterior portions of the left hemisphere, was singularly uninvolved.

The net result of these pathological changes was that the basilar part of the pons and the central cephalic portion of the tegmentum, as well as the left internal capsule and thalamus, were largely destroyed, few apparently functional neurones or axones remaining in these regions (Fig. 2). Of parenthetical interest was the finding at autopsy of an acute perforation of the stomach and an actively eroding ulcer of the duodenum.

CASE 2.—A. C., a girl aged 20, sustained a severe head injury in May, 1948, from which she was said never to have regained consciousness. When examined on Aug. 26, 1948, she was found to be confined to bed, completely helpless and covered with decubitus ulcers. At times, she would open her eyes, but never did she display any evidence suggesting that she was in touch with her surroundings. She uttered no sounds and was unable to chew food, although liquids placed in her mouth were swallowed. Occasionally, spontaneous smacking or chewing movements occurred. Pupillary abnormalities and conjugate deviation of the eyes were present. Her muscular condition was that of spasticity in flexion; and, while reflex withdrawal and random movements occurred bilaterally, particularly after painful stimuli, no voluntary or adaptive movements were made. The deep reflexes were diffusely hyperactive, and pathological toe signs were present.

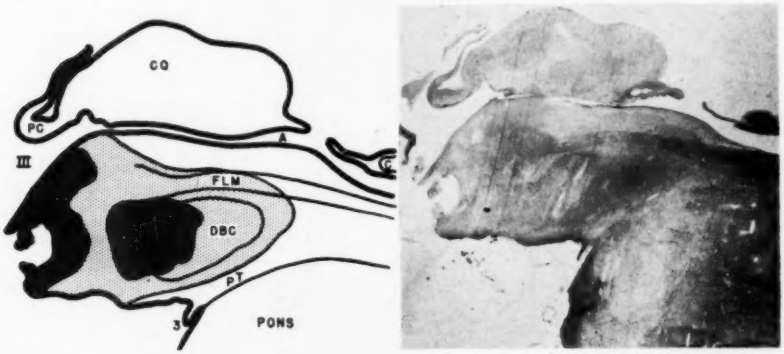

Fig. 3 (Case 2).—The midsagittal diagrammatic outline of the brain stem on the left shows the areas of softening (black) and gliosis (dots) in the tegmentum, apparent in the photomicrograph on the left (thionine stain), in Patient A. C.

A indicates aqueduct; *C*, cerebellum; *CQ*, corpora quadrigemina; *DBC*, decussation of the brachium conjunctivum; *FLM*, fasciculus longitudinalis medialis; *PC*, posterior commissure; *PT*, pontine tegmentum; *III*, third ventricle; *3*, third nerve.

An electroencephalogram made at this time showed diffuse cortical dysrhythmia characterized by high-voltage slow activity. A pneumoencephalogram showed evidence of mild ventricular dilatation throughout.

The patient died at home in December, 1948, approximately seven months after injury. Her family reported that she had remained in a state identical with that recorded above for the remainder of her survival period.

Autopsy.—Details of necropsy, performed privately, were not available except for the statement by the examining physician that there was no gross abnormality of the brain. An alert house officer, however, was able to retrieve sufficient portions of the discarded brain to verify that there was minimal evidence of atrophy or injury to the cerebral hemispheres and to indicate that the major disturbance involved the brain stem and the basal ganglia. On the left side an area of softening, 2 by 3 cm., in the left globus pallidus involved the anterior limb of the internal capsule and the caudate nucleus. Tiny softenings were also seen in the right pulvinar, in the substantia nigra, and in two or three areas of the cortex, but none of these was larger than 5 mm. in diameter.

In the anterior portion of the tegmentum there were two areas of softening, 1.5 and 3 mm. in diameter, respectively. Microscopically, however, the entire tegmentum was replaced by glial tissue and by phagocytes, there being essentially no normal-appearing neurones for the cephalic 1.2 cm. of the area, between the substantia nigra and the periaqueductal gray matter (Fig. 3).

Case 3.—R. C., a man aged 40, was struck by an automobile on Oct. 23, 1946, and was rendered permanently unconscious. Shortly thereafter he was found to be spastic in all extremities and to show a Babinski sign bilaterally. Bilateral trepanation showed diffuse edema, but there was no localized collection of blood.

The patient remained in essentially the same condition throughout the period of his survival. After an initial period of several weeks, in which he was completely comatose, he had definite intervals of waking and sleeping, but during his waking periods there was no movement other than reflex withdrawal of the extremities and no indication that he was aware of his surroundings. It was necessary to feed him by a Levin tube and to maintain vigorous nursing attention so that decubitus ulcers and respiratory, as well as urinary, infections could be avoided or improved. Electroencephalograms obtained five and nine months after injury were essentially identical records, characterized by diffuse high-voltage slow activity. Just prior to his death, in July, 1947, some nine months after injury, his condition was essentially unchanged from what it had been several weeks after his admission to the hospital.

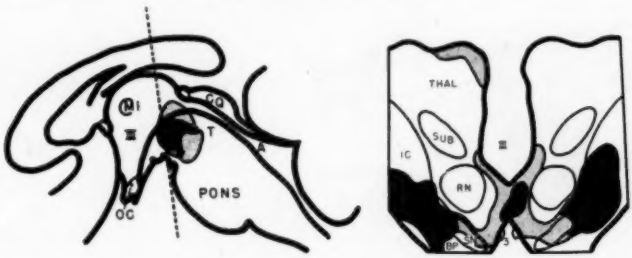

Fig. 4 (Case 3).—The midsagittal diagram of the brain stem on the left shows the approximate location and extent of softening (black) and gliosis (dots) in Patient R. C. The level of the cross section on the right is designated by the dotted line.

BP indicates brachium pontis; *IC*, internal capsule; *OC*, optic chiasma; *RN*, red nucleus; *SN*, substantia nigra; *SUB*, subthalamic nucleus, and *THAL*, thalamus. Other abbreviations are as in Figures 2 and 3.

Examination of Brain.—The brain was retrieved from a coroner's physician after it had been sectioned. The gross findings in an examination available to us were softenings or brownish discolorations in the left uncus, the midbrain, with involvement of the substantia nigra, the right hypothalamus and subthalamus, and the right cuneus.

Review of the microscopic sections verified the aforementioned lesions. Certainly, the lesions in the uncus and cuneus were small, while those in the midbrain appeared to be more significant. Microscopic softenings, centering in the basis pedunculi bilaterally, involved the substantia nigra on each side. Extending medially from these areas, and involving the major portion of the tegmentum, was a zone essentially devoid of normal nerve cells and containing patchy areas of gliosis, encephalomalacia, and phagocytosis. Elsewhere, particularly in the thalamus, excessive numbers of oligodendrocytes, frequently clumped around chronically degenerated neurons, were present (Fig. 4).

Case 4.—H. H., a man aged 31, had a bronchoscopy on March 19, 1951, for a chest disorder of two months' duration. During this procedure cardiac arrest occurred, and the pulse was reestablished some seven minutes later by cardiac massage. He remained essentially comatose, however, for the rest of his survival period, of seven months.

During this period, after an initial period of six weeks, when he was totally unresponsive, he slept most of the time but had intervals when he appeared awake. At these times, however, he was completely akinetic, maintaining a posture of spastic hyperflexion. At no time was there any evidence that he was aware of his surroundings, although he would blink occasionally on loud noise or briefly follow a light with his eyes. Pathological reflexes were present bilaterally. An electroencephalogram made four months after onset of his coma was flat and featureless, a satisfactory tracing being apparently impossible to obtain because of movement artifact.

Autopsy.—Grossly the brain did not appear abnormal, and the ventricles were not dilated. Sections made elsewhere than in the brain stem, so as to preserve this structure for serial sectioning, showed no obvious abnormality. The block, comprising the thalamus and the brain stem, however, was markedly flattened and atrophic.

This block of the cephalic portion of the brain stem was sectioned serially, alternate sections being stained by the Weil and by the thionine method. Microscopically, the entire dorsal half

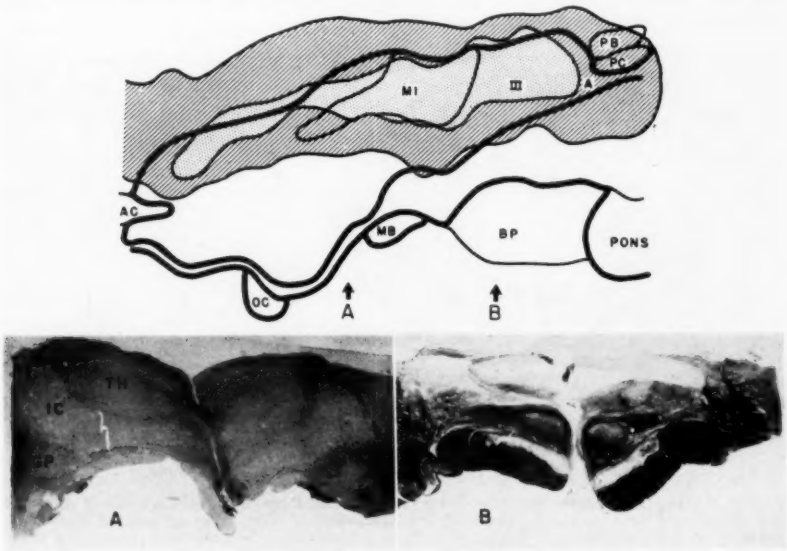

Fig. 5 (Case 4).—The upper figure is a midsagittal diagram reconstructed from serial sections of the brain stem in Patient H. H. Midline destruction of functional tissue is indicated by the dotted area, while lateral extension of these changes is designated by cross hatching. The lower photomicrographs, *A* (thionine stain) and *B* (Weil stain), are taken from the areas indicated on the reconstruction (arrows). Note destruction in the dorsal halves of the figure and cross sections. *AC* indicates anterior commissure; *PB*, pineal body, *TH*, thalamus, and *GB*, globus pallidus. Other abbreviations are as in Figures 2, 3, and 4.

of this structure showed pronounced alteration, presumably the result of anoxia. Involved was the dorsal thalamus, principally the medial, anterior, ventrolateral, ventroanterior, and pulvinar nuclei, as well as the caudate nucleus and the lateral portion of the internal capsule. Relatively spared were the centrum medianum, the intralaminar and relay nuclei, the globus pallidus, and, to a less extent, the midline nuclei of the thalamus. The cephalic portion of the tegmentum and the structures anterior to those mentioned above showed surprisingly little alteration (Fig. 5).

The microscopic changes were essentially similar in all the areas involved. The vessels frequently showed conspicuous perithelial thickening, varicosity, and often cuffing with lympho-

cytes. Areas of intense gliosis, involving in the main oligodendrocytes, but also astrocytes, essentially replaced completely nuclear masses, no recognizable neurones being present. Interspersed throughout these gliotic areas were patchy regions in which no cellular elements were visible. In the Weil preparations myelin disintegration was apparent in the areas so involved, particularly in the internal capsule.

In the ventral half of the block such changes were also recognizable, but to a minimal degree. Glial tissue was more prominent than normal, and chronic neuronal change was recognizable, but the nuclear patterns were undisturbed.

The cortex was particularly free from microscopic change. Occasional neurones showed degeneration or had disappeared, but vascular or gliotic changes were not present.

CASE 5.—M. P., a man aged 59, was admitted to the hospital in February, 1949, because of progressive mental deterioration. For many years he had had complaints referable to his stomach, for which a gastric resection was done in June, 1948. Subsequently, unsteadiness in walking, failure of vision, generalized hypalgesia, and increasing delirium progressed until hospitalization was necessitated.

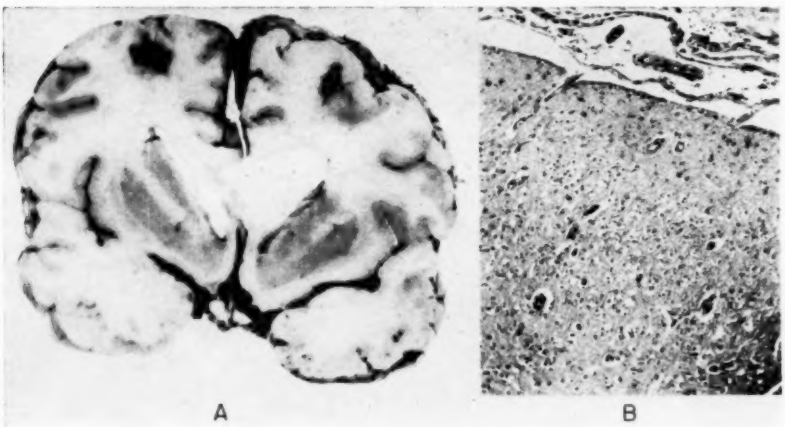

Fig. 6.—In *A*, a cross section of the brain in Patient M. P., note the diffuse areas of softening and atrophy of the cortex. *B* (hematoxylin-eosin stain) is taken from an area of the cortex showing no gross evidence of lesion. The cortical architecture is completely destroyed.

On examination, he was found to be grossly confused and disoriented. Argyll Robertson pupils were noted, as were bilateral palmomental signs, grasp reflexes, hyperreflexia, pathological toe signs, and signs of meningeal irritation. The spinal fluid pressure was not elevated, and serologic reactions were negative, but as many as 394 cells per cubic millimeter were present at various times, and the colloidal gold curve was of a dementia-paralytica type. The electroencephalogram showed diffuse high-voltage slow-wave activity, predominantly in the frontal regions. A ventriculogram revealed marked dilatation of all ventricles, with evidence of rather severe cortical atrophy.

From the end of February until he died, on July 6, 1949, the patient was completely mute, akinetic, and apparently comatose, although there were brief periods during the day when he would open his eyes. Even at these times he was completely unresponsive to external stimuli and, being completely helpless, required tube feeding and total nursing care.

Autopsy.—Examination of the brain showed diffusely thickened leptomeninges, with flattening of the gyri and dilatation of the ventricles. Multiple areas of softening were seen involving largely the cortex or the subcortical white matter. Microscopically, the major abnormalities were confined almost entirely to the leptomeninges and cortex. The leptomeninges were

thickened and fibrotic, containing phagocytic cells as well as lymphocytes and plasma cells. The cortex was thinned throughout, all degrees of neuronal degeneration being present and normal cortical architecture being completely absent. Astrocytic proliferation was intense, and perivascular round-cell infiltration was present everywhere. The vessels themselves were thickened, and many new capillaries were seen. The same changes were present in the peripheral regions of the medulla, but the brain stem, thalamus, and white matter were relatively uninvolved. The diagnosis was considered to be granulomatous meningoencephalitis suggestive of meningovascular syphilis, but the etiological cause could not be established (Fig. 6).

COMMENT

The clinical appearances of the three patients with significant injury to the cephalic portion of the tegmentum (F. T., A. C., R. C.) were strikingly similar. All, for example, showed hypokinesis, spasticity, altered pupillary and ocular-muscle activity, pathological reflexes, apparent insensitivity to sensory stimuli, mutism, loss of deglutition, impaired sphincter control, and complete amentia. Characteristically, the patients appeared to be asleep, a state in which they remained most of the time. Occasionally, particularly when stimulated painfully, they would open their eyes, but usually after a matter of minutes would resume the appearance of sleep. During the fleeting wakeful periods the patients would not attend to sight, sound, touch, taste, or smell stimuli, and no purposeful movements were ever observed. Evacuation was performed reflexly. All feedings and fluids were administered by stomach tube. In summary, the patients were mentally and emotionally inert, giving no indication of any contact whatever with their surroundings, to which they were unable to respond adaptively. During the chronic phase of their disease the spinal fluid pressure was not elevated; blood pressure, pulse and respirations were normal, and other visceral functions were apparently sufficiently intact to sustain life for as long as nine months. Moreover, the electroencephalograms in all cases displayed the same synchronous characteristics.

Various lesions observed at autopsy in the cortex, cerebral peduncles, basal ganglia, and ventral portion of the mesencephalon readily explain the spasticity, abnormal reflexes, and ocular changes, and possibly other symptoms presented by these patients. They do not, however, explain the total mental abolition observed in each instance. The lesion common to three patients was that in the central cephalic portion of the brain stem. It seems justifiable, therefore, on clinicopathological grounds to view this injury with suspicion as an etiological factor in the production of the inert, adaptively unresponsive, helpless state to which these patients were reduced. There were certainly other clinical evidences of mesencephalic injury, and information is accumulating rapidly which tends to demonstrate that conscious awareness is most easily disturbed by lesions in this area.

During the past 25 years there has been rather general agreement that the area essential for the maintenance of "consciousness" lies in or near the diencephalon, but the extent of this area and the mechanisms involved have been more controversial. Fulton and Bailey [3]; von Economo,[4] and Bailey, Buchanan, and Bucy [5] on the basis

3. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1, and 45 (Feb.) 1929.

4. von Economo, C.: Sleep as a Problem of Localization, J. Nerv. & Ment. Dis. **71**:249-259 (March) 1930.

5. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

of clinical observations, concluded that the critical area involved in this condition lay in the brain stem about the aqueduct of Sylvius. Penfield [6] and Cairns and coworkers [7] agreed with this localization in general but indicated the probability of hypothalamic involvement. Ranson,[8] on the basis of animal experimentation, implicated directly the posterior hypothalamus, with which concept Fulton,[9] Globus,[10] and Davison and Demuth [11] agreed. Bailey and Davis [12] were able to produce animals with arrest of consciousness by making lesions in the periaqueductal gray matter. Dandy [13] considered the striate body to be the "center of consciousness," but later Meyers [14] disproved this concept. Alford [15] suggested that destruction of the left thalamus resulted in the "abolition of mental capacity," while Heid and Lasky,[16] as well as Brockman,[17] described patients in brief "coma" whose significant lesions were in both thalami. More recently Thompson and Nielsen [18] and Thompson [19] have suggested that the entire area where the mesencephalon, subthalamus, and hypothalamus meet is essential to the engram system responsible for crude consciousness. Here, then, is variety of suggestions concerning the area responsible for alterations in "consciousness," but of significance is the fact that in essentially every case the cephalic portion of the brain stem is implicated.

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6. Penfield, W.: The Cerebral Cortex in Man: I. The Cerebral Cortex and Consciousness, Arch. Neurol. & Psychiat. **40**:417-442 (Sept.) 1938.

7. Cairns, H.; Oldfield, R. C.; Pennybacker, J. B., and Whitteridge, D.: Akinetic Mutism with Epidermoid Cyst of the Third Ventricle, Brain **64**:273-290 (Dec.) 1941.

8. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1-23 (Jan.) 1939.

9. Fulton, J. F., cited by Globus, J. H.: Probable Topographic Relations of the Sleep-Regulating Center, Arch. Neurol. & Psychiat. **43**:125-138 (Jan.) 1940.

10. Globus, J. H.: Probable Topographic Relations of the Sleep-Regulating Center, Arch. Neurol. & Psychiat. **43**:125-138 (Jan.) 1940.

11. Davison, C., and Demuth, E. L.: Disturbances in Sleep Mechanism: A Clinicopathologic Study; III. Lesions at the Diencephalic Level (Hypothalamus), Arch. Neurol. & Psychiat. **55**:111-125 (Feb.) 1946; A Clinicopathologic Study; IV. Lesions at the Mesencephalometencephalic Level, ibid. **55**:126-133 (Feb.) 1946.

12. Bailey, P., and Davis, E. W.: Effects of Lesions of the Periaqueductal Grey Matter in the Cat, Proc. Soc. Exper. Biol. & Med. **51**:305-306 (Nov.) 1942.

13. Dandy, W. E.: The Location of the Conscious Center in the Brain: The Corpus Striatum, Bull. Johns Hopkins Hosp. **79**:34-58 (July) 1946.

14. Meyers, R.: Dandy's Striatal Theory of "The Center of Consciousness": Surgical Evidence and Logical Analysis Indicating Its Improbability, A. M. A. Arch. Neurol. & Psychiat. **65**:659-671 (June) 1951.

15. Alford, L. B.: The Localization of the Mental Functions: A New Conception, South. M. J. **43**:262-264 (March) 1950.

16. Heid, J. B., and Lasky, I.: Thalamic Lesions and Coma, Bull. Los Angeles Neurol. Soc. **11**:91-93 (March-June) 1946.

17. Brockman, N. W.: Site of Minimal Lesion to Produce Coma, Bull. Los Angeles Neurol. Soc. **11**:90-91 (March-June) 1946.

18. Thompson, G. N., and Nielsen, J. M.: Area Essential to Consciousness: Cerebral Localization of Consciousness as Established by Neuropathological Studies, J. A. M. A. **137**:285 (May 15) 1948.

19. Thompson, G. N.: Cerebral Area Essential to Consciousness, Bull. Los Angeles Neurol. Soc. **16**:311-334 (Dec.) 1951.

A somewhat more divergent opinion is expressed concerning the mechanism involved in "sleep" or in "consciousness." Deafferentation of the cortex has been suggested by Kleitman and Camille [20] and by Bremer [21] as responsible for states of depressed awareness or sleep. A similar, if somewhat more complex, suggestion is that of Cairns and associates,[7] who considered it possible "that consciousness depends on the synthesis of impressions from the outside world with those from the interior of the body and that this is one of the main functions of the hypothalamic-thalamic system and its cortical connections." Alteration in function of the hypothalamus has a number of advocates. Ranson [8] attributed somnolence to the elimination of excitation caused by hypothalamic activity, while Fulton [9] suggested that manifestations of parasympathetic predominance characterized this state. In this connection, Globus [10] stated the belief that cell aggregations in the lateral hypothalamic areas function as a sleep-regulating center, while Hess [22] reported the production of sleep at will by stimulating areas in the diencephalon, considering this state to be due to a reflex inhibitory influence which the autonomic nervous system exerts on the centers of the animal's system. With such an inhibitory theory of sleep von Economo [4] apparently agreed, but Bremer [23] refuted the existence of a sleep center (*centre hypnogène*), supporting, rather, the concept that somnolent states result from a depression of function of the awakening mechanism. Recently, Thompson [19] has indicated his belief that lesions in the cephalic portion of the tegmentum produce coma by interrupting fibers from cells in the posterior portion of the third ventricle and the periaqueductal gray matter to the hypothalamus and thalamus on the opposite side.

In general, the importance of the cortex in "conscious" states has been more or less tacitly implied in previous discussions, although cortical influence is frequently not mentioned and opinion has been expressed to the effect that it is not critically involved in waking-sleeping functions. Thus, Penfield [6] stated: "A priori, there seems to be no reason that the neural mechanisms essential to consciousness should migrate outward into the newly exfoliative hemisphere." Similarly, Nielsen and Thompson [24] pointed to the apparently normal waking and sleeping states demonstrated by anencephalic monsters. On the other hand, Jefferson,[25] recognizing the fundamental importance of the cephalic part of the brain stem in consciousness, conceded that for "full consciousness in the psychologist's sense" the cortex was necessary.

Experiments by Magoun and his associates on the cephalic brain-stem structures during the past 10 years have illuminated to some degree certain aspects of the arousing response in animals. It has been shown that there exists in the central

20. Kleitman, N., and Camille, N.: Studies on the Physiology of Sleep: VI. The Behavior of Decorticated Dogs, Am. J. Physiol. **100**:474-480 (May) 1932.

21. Bremer, F.: L'activité cérébrale et le probléme physiologique du sommeil, Boll. Soc. ital. biol. sper. **13**:271-290, 1938.

22. Hess, W. R.: The Autonomic Nervous System: Sleep as a Regulating Process, Lancet **2**:1259-1261 (Dec. 10) 1932.

23. Bremer, F.: Le probléme physiologique du sommeil, Medicina (Parma) **5**:589-612, 1951.

24. Nielsen, J. M., and Thompson, G. N.: The Engrammes of Psychiatry, Springfield, Ill., Charles C Thomas, Publisher, 1947, pp. 16-17.

25. Jefferson, G.: The Nature of Concussion, Brit. M. J. **1**:1-5 (Jan. 1) 1944.

portion of the tegmentum, the subthalamus and hypothalamus, and the medial thalamus an area capable of mass excitation by peripheral stimuli delivered to somatic or visceral nerves.[26] When this area is excited in such a fashion, or directly by means of a probing electrode, changes occur in the behavior, as well as in the electrocortical activity, of the animal identical with those seen in its arousal from sleep.[27] By virtue of such apparent functions in the "waking responses," this area has been called the reticular activating system. It has further been shown that this system exerts its influence on the entire cortex via pathways which course fountain-like, probably by multiple relays, through the thalamus and the internal capsule.[28]

Destruction of this activating system in cats and monkeys has produced in animals behavioral and electrocortical states identical so far as can be determined with those apparent in the comatose human being.[29] The depth and persistence of such coma appeared to correlate directly with the extent of the total active area of the system destroyed, complete destruction, however, being incompatible with survival. Lesions of similar magnitude in the same general region, but sparing the major portion of the activating system, did not produce such an effect. Even when the lesion involved the entire posterior hypothalamus, animals surviving sufficiently long to recover from the operative procedure frequently exhibited normal wakefulness.[30]

On the basis of these observations, it is suggested that the similar unresponsive state observed in all five cases reported here resulted from disturbance of an activating process mediated by the brain stem. This disturbance occurred predominantly in the reticular activating system in three cases, in its subcortical radiations in one (Case 4) and in its cortical terminus in one (Case 5).

These data suggest the inadvisability of considering the reticular activating system as a "center of consciousness" or a "center of wakefulness," in that afferent impulses are required to excite it and the manifestations of its activity are expressed only through its influences on other subcortical structures and on the entire cortex. In the absence of such higher centers, this system would appear to have no more intrinsic function than has the lateral geniculate nucleus without the visual receptive area of the cortex. The area would seem to serve, therefore, as a complex relay system energizing in some way normal activity of more highly developed centers the integrated function of which is essential to the adaptive behavior of the waking human being.

It is apparent, then, that in a concept of human "consciousness" concerning such an activating system the integrity of the cortex is implicit. While it is true that

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26. (*a*) Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Collateral Afferent Excitation of Reticular Formation of Brain Stem, J. Neurophysiol. **14**:479-496 (Nov.) 1951. (*b*) French, J. D.; von Amerongen, F. K., and Magoun, H. W.: An Activating System in the Brain Stem of the Monkey, A. M. A. Arch. Neurol. & Psychiat. **68**:577-604 (Nov.) 1951.

27. French and others.[26b] Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455-473 (Nov.) 1949.

28. Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Ascending Conduction in Reticular Activating System with Special Reference to the Diencephalon, J. Neurophysiol. **14**:461-477 (Nov.) 1951.

29. Lindsley and others.[1] French and Magoun.[2]

30. Porter, R. W.: Unpublished data.

decorticate carnivores and, to a less extent, primates exhibited some degree of behavioral alertness, it is difficult to believe that a similar condition in man, with his critical reliance on highly integrated function, would be compatible with normal waking awareness. In this regard, Bailey [31] has stated:

> To my way of thinking, mind is simply a name which we give to the functioning of the cerebral cortex. Perhaps the cortex has to be activated by something deeper in the nervous system, much as a radio tube has to be heated before it begins to conduct, but mind is essentially the functioning of the cerebral cortex.

It would seem to be necessary at this point to reexamine a possible conflict in terminology denoting the physiological and pathological conscious states of "sleep" and "coma," because patients in this series have exhibited brief periods of wakefulness, although these were unattended by any evidence of conscious awareness. In their studies on the physiology of sleep, Kleitman and Camille [20] found that decorticate dogs were incapable of a diurnal sleep cycle, reverting instead to a state characteristic of puppyhood, in which they would awaken and sleep many times a day, presumably on a vegetative, rather than an externally adaptive, basis. These authors added:

> Since puppies and new-born infants are, physiologically speaking, without a cortex, we are led to the inevitable conclusion that diurnal sleep depends for its development, and once developed for its maintenance, upon a physiologically active cerebral cortex.

If such an analogy between animal and man is acceptable, it must be admitted that the sleeping and waking processes, while still possible, are grossly altered in the decorticate human being and revert, as in the animal, to those characteristics of the newborn. Indeed, there is much in the appearance of the patients here reported, as well as in their synchronous electrocortical activity, that would make such a comparison with the infant an apt one. It remains, then, to decide whether or not the decorticate adult, like the infant, still capable of awakening and sleeping, is "conscious" or "stuporous." To describe pathological sleep resulting from injuries to the cephalic portion of the brain stem, Jefferson [25] coined the term "parasomnia," "a state in which there is no response to stimuli, verbal or mechanical, except those of a reflex nature." Such a term would seem to be useful, although it does not differentiate perhaps between states in which patients are totally unarousable and those in which waking without awareness can occur.

It must be concluded, therefore, that the activating system in the cephalic portion of the brain stem, receiving its energy from the visceral and somatic periphery, is capable of exciting subcortical structures, principally the mesial part of the thalamus and the hypothalamus, to activity, thus permitting waking and sleeping on a crude and infantile basis. It also exerts its influence on the cortex and is responsible, then, for diurnal wakefulness and for adaptive behavior characteristic of the "conscious" adult. Subtotal injury to this activating system or to its cortical reflections would seem to render the neopallium functionally impotent and incapable of the latter highly developed attributes; a person so afflicted is said to be "stuporous," or "parasomnic," but is still capable of crude awakening and sleeping. Total destruction of this system would not appear to be compatible with prolonged survival in

31. Bailey, P., in discussion on Jasper, H.; Ajmone-Marsan, C., and Stoll, J.: Corticofugal Projections to the Brain Stem, A. M. A. Arch. Neurol. & Psychiat. **67**:168 (Feb.) 1952.

man, as it was not in animals. Under such circumstances a person loses even the crude or vestigial waking response during his limited survival and is called "comatose."

SUMMARY

The clinical and pathological findings in five patients who displayed profound alteration in "consciousness" for periods ranging from four to nine months are reviewed. In three of the five patients lesions were so situated as to destroy a major portion of the reticular activating system in the cephalic part of the brain stem. In another case, the pathological disturbance was greatest more cephalad, in the dorsal portion of the thalamus and neighborhood areas, while in still another case the entire cortical mantle was most seriously involved.

Considerations concerning a possible explanation for the disturbance in conscious awareness manifested by these patients are discussed in the light of previous reviews of the subject and of animal experimentation involving areas of the brain comparable to those found to be disturbed in this study.

The evidence suggests that such alteration as that described results from a deficiency of exciting influences on subcortical and cortical structures, either by destruction of the reticular activating system itself or by its isolation from higher functional areas.

A CEREBELLAR COMPONENT OF CONVULSIVE MANIFESTATIONS

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IT IS GENERALLY accepted that experimental stimulation of the cerebellum does not result in epileptiform convulsions. Furthermore, as stated by Penfield and Erickson,[1] "there is no good clinical evidence that lesions of the cerebellum modify or produce any increased tendency to seizures."

Cannon [2] and Stavraky,[3] with their associates, have found that lesions within the central nervous system which lead to partial isolation of definite groups of neurones render them supersensitive to various forms of stimulation, this taking place in the absence of any detectable cytological changes in the denervated neurones (Cook, Walker, and Barr [4]). In the case of convulsant agents it was shown by Stavraky [3a] and by Drake and Stavraky [3d,e] that, in chronic cats, after removal of

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1. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Charles C Thomas, Publisher, Springfield, Ill., 1941, p. 218.

2. Cannon, W. B., and Haimovici, H.: Sensitization of Motoneurones by Partial "Denervation," Am. J. Physiol. **126**:731-740, 1939. Cannon, W. B.; Rosenbleuth, A., and Garcia-Ramos, J.: Sensibilización de las neuronas espinales por denervacio parcial, Arch. Inst. cardiol. México **15**:327-348, 1945. Rosenbleuth, A.; Garcia-Ramos, J., and Cannon, W. B.: Los reflejos espinales extensores cruzado e ipsilateral, ibid. **15**:401-454, 1945.

3. (*a*) Stavraky, G. W.: Some Aspects of the Effects of Intravenous Injections of Acetylcholine on the Central Nervous System, Tr. Roy. Soc. Canada (Sect. V, Biol. Sc.) **37**:127-139, 1943; (*b*) Action of Adrenaline on Spinal Neurones Sensitized by Partial Isolation, Am. J. Physiol. **150**:37-45, 1947. (*c*) Fisher, S. M., and Stavraky, G. W.: Effects of Acetyl-Beta-Methyl-Choline in Human Subjects with Localized Lesions of the Central Nervous System, Am. J. M. Sc. **208**:371-380, 1944. (*d*) Drake, C. G., and Stavraky, G. W.: Effect of Convulsant Agents on Partially Denervated Neurones of the Central Nervous System, Federation Proc. **7**:29, 1948. (*e*) Drake, C. G.: Effect of Convulsant Agents on Partially Denervated Neurones in the Central Nervous System, Thesis, University of Western Ontario, London, Ont., Canada, 1947, pp. 1-63. (*f*) Drake, C. G., and Stavraky, G. W.: An Extension of the "Law of Denervation" to Afferent Neurones, J. Neurophysiol. **11**:229-238, 1948. (*g*) Teasdall, R. D., and Stavraky, G. W.: Response of Deafferented Neurones of Spinal Cord to Impulses Reaching Them from Higher Levels of Central Nervous System, Federation Proc. **7**:123, 1948; (*h*) Postural Reflexes in Deafferented Limbs of the Cat, ibid. **8**:155, 1949; (*i*) Effect of Section of the Corpus Callosum on Experimental Convulsions, ibid. **9**:124-125, 1950. (*j*) Hughes, R. A.; Stavraky, G. W., and Teasdall, R. D.: A Study of the Mechanism of Reversal of Spinal and Bulbar Reflexes, Tr. Roy. Soc. Canada (Sect. V, Biol. Sc.) **44**:39-60, 1950.

4. Cook, W. H.; Walker, J. J., and Barr, M. L.: A Cytological Study of Transneuronal Atrophy in the Cat and Rabbit, J. Comp. Neurol. **94**:267-292, 1951.

one frontal lobe or after semidecerebration, intravenous injections of acetylcholine, camphor, or pentylenetetrazol U. S. P. (metrazol®) resulted in an asymmetrical convulsion, in which tonic manifestations greatly predominated on the denervated side. The latter investigators were able to confirm the earlier findings of Pike and Elsberg [5] and of Dandy and Elman [6] that during the convulsion such cats often fell, rolled, and circled away from the side of the cerebral ablation.

The view that the cerebellum may influence motor activity is firmly established. Besides its demonstration in the study of clinical cases and of animals with various cerebellar ablations, this was shown in experiments in which the cortex and nuclei of the cerebellum were stimulated both in decerebrate and in anesthetized animals (Sherrington [7]; Miller and Banting [8]; Miller and Laughton [9]; Hare, Magoun, and Ranson [10]; Clark [11]; Nulsen, Black, and Drake [12]; Snider and Magoun [13]; Snider, McCulloch, and Magoun [14]; Moruzzi [15]; Chambers and Sprague,[16] and others). In view of the foregoing observations, it seemed plausible that removal of various parts of the cerebellum would sensitize motor mechanisms with which the cerebellum was connected, and that such a sensitization would show its effect on chemically induced convulsions, the latter form of stimulation being particularly effective in the case of partially isolated motor neurones. This hypothesis was made the subject of the present investigation.

METHODS

In 25 cats unilateral ablations of the cerebellum were carried out. The extent and location of the lesions varied as follows: Complete semicerebellectomy with a concomitant lesion of the ipsilateral bulbar structures (damage of the vestibular nucleus, as revealed by subsequent histological examination) was done in four cats. In seven animals semicerebellectomy without any injury to the bulbar structures was performed. (In three cats semicerebellectomy was complete; in four other animals it was less extensive but always involved the cerebellar nuclei.)

5. Pike, F. H., and Elsberg, C. A.: Studies on Epilepsy: II. Occurrence of Clonic Convulsive Seizures in Animals Deprived of the Cerebral Motor Cortex, Am. J. Physiol. **72**:337-342, 1925.

6. Dandy, W. E., and Elman, R.: Studies in Experimental Epilepsy, Bull. Johns Hopkins Hosp. **36**:40-49, 1925.

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8. Miller, F. R., and Banting, F. G.: Observations on Cerebellar Stimulations, Brain **45**:104-112, 1922.

9. Miller, F. R., and Laughton, N. B.: Functions of the Cerebellar Nuclei as Determined by Faradic Stimulation, Arch. Neurol. & Psychiat. **19**:47-72, 1928.

10. Hare, W. K.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of the Interior of the Cerebellum in the Decerebrate Cat, Am. J. Physiol. **117**:261-266, 1936.

11. Clark, S. L.: Responses Following Electrical Stimulation of the Cerebellar Cortex in the Normal Cat, J. Neurophysiol. **2**:19-35, 1939.

12. Nulsen, F. E.; Black, S. P. W., and Drake, C. G.: Inhibition and Facilitation of Motor Activity by the Anterior Cerebellum, Federation Proc. **7**:86-87, 1948.

13. Snider, R. S., and Magoun, H. W.: Facilitation Produced by Cerebellar Stimulation, J. Neurophysiol. **12**:335-345, 1949.

14. Snider, R. S.; McCulloch, W. S., and Magoun, H. W.: A Cerebello-Bulbo-Reticular Pathway for Suppression, J. Neurophysiol. **12**:325-334, 1949.

15. Moruzzi, G.: Paleocerebellar Inhibition of Vasomotor and Respiratory Carotid Sinus Reflexes, J. Neurophysiol. **3**:20-32, 1940; Cerebellar Physiology, Charles C Thomas, Publisher, Springfield, Ill., 1950, pp. 6-70.

16. Chambers, W. W., and Sprague, J. M.: Differential Effects of Cerebellar Anterior Lobe Cortex and Fastigial Nuclei on Postural Tonus in the Cat, Science **114**:324-325, 1951.

In five animals the cerebellar nuclei were destroyed by means of a monopolar needle electrode placed with the Horsley-Clarke stereotaxic apparatus (multiple applications of a current of 3 ma. for 30 seconds inducing the lesion). In four animals one-sided lesions of the cortex of the flocculonodular lobe were made (two cats had the entire flocculonodular lobe removed, and in two animals only ablation of the left half of the nodulus and uvula was carried out). In three cats one-sided decortication of the anterior lobe was done. In one animal the left side of the neocerebellum was removed, and in another the left half of the corpus cerebelli was destroyed.

After recovery from the operation, the animals were given injections of convulsant doses of pentylenetetrazol and acetylcholine at intervals of one to three weeks, the period of observation lasting up to 15 months. Pentylenetetrazol and acetylcholine were dissolved in distilled water and freshly prepared each time. Pentylenetetrazol was used in a concentration of 25 mg. per milliliter, and acetylcholine chloride was used in a concentration of 0.5 mg. per milliliter. The injections of both the acetylcholine and the pentylenetetrazol were made routinely into the internal saphenous vein of the hindlimb; a number of the convulsions were photographed with a moving-picture camera, thus permitting an analysis of the rapid movements of the animals.

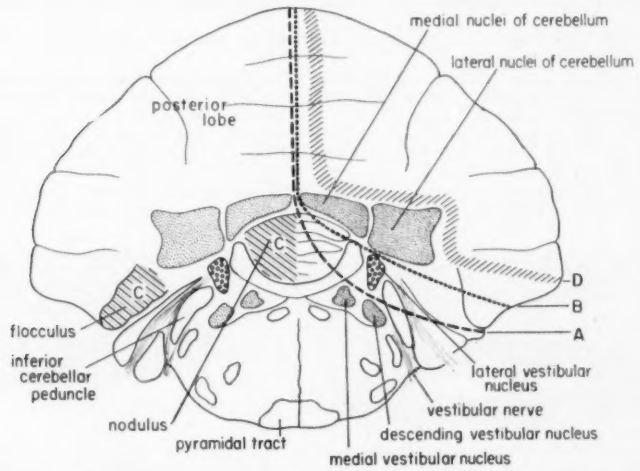

Fig. 1.—Cross section of the cerebellum and brain stem of the cat, showing schematically the extent of the ablation carried out in the four groups of animals described in the text.

A, extent of the semidecerebellation with involvement of the vestibular nucleus; *B*, extent of the semidecerebellation or of destructive lesions in the cerebellar nuclei without any detectable involvement of the vestibular nuclei; *C*, ablation of the flocculonodular lobe (lesions limited to cerebellar cortex); *D*, decortication of the corpus cerebelli without involvement of the cerebellar or vestibular nuclei and not extending to the flocculonodular lobe.

At the conclusion of the study the cats were perfused with isotonic 10% formalin according to the technique of Koenig, Groat, and Windle,[17] and the brain was sectioned and stained with cresyl violet for cellular detail. Weil's method was used for fiber tracts and Victoria blue for scar tissue.

RESULTS

In accordance with the pattern of convulsions induced by pentylenetetrazol and by acetylcholine, the observations are divided into three groups. The first group includes animals in which half the cerebellum was removed, with concomitant

17. Koenig, H.; Groat, R. A., and Windle, W. F.: A Physiological Approach to Perfusion —Fixation of Tissues with Formalin, Stain Technol. **20**:13-22 1945.

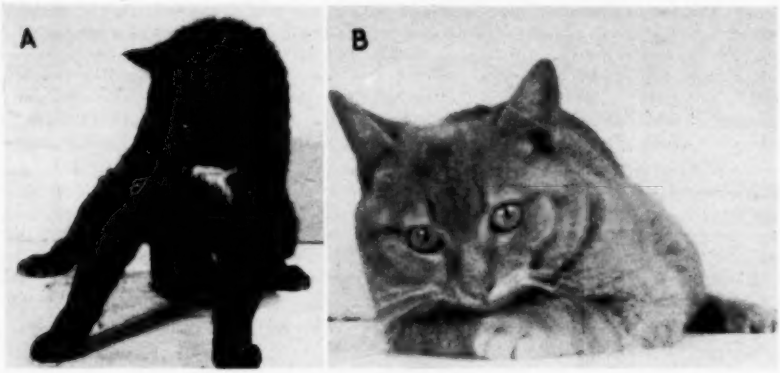

Fig. 2.—Typical attitude of chronic semidecerebellate cats with and without extension of the lesion to the bulbar nuclei.

A, cat with left semicerebellation of 2½ months' standing with a degenerative change in the left vestibular nuclei. (Extent of the actual ablation and degree of involvement of the vestibular nuclei are shown in Figure 4.)

B, cat with semidecerebellation of one week's standing with complete extirpation of the cerebellar nuclei but without any change in the cells of the vestibular nuclei. (Extent of the actual ablation is shown in Figure 5.)

The same posture was produced by lesions of the cerebellar nuclei only and by localized ablation of the flocculonodular lobe without damage to the cerebellar or vestibular nuclei.

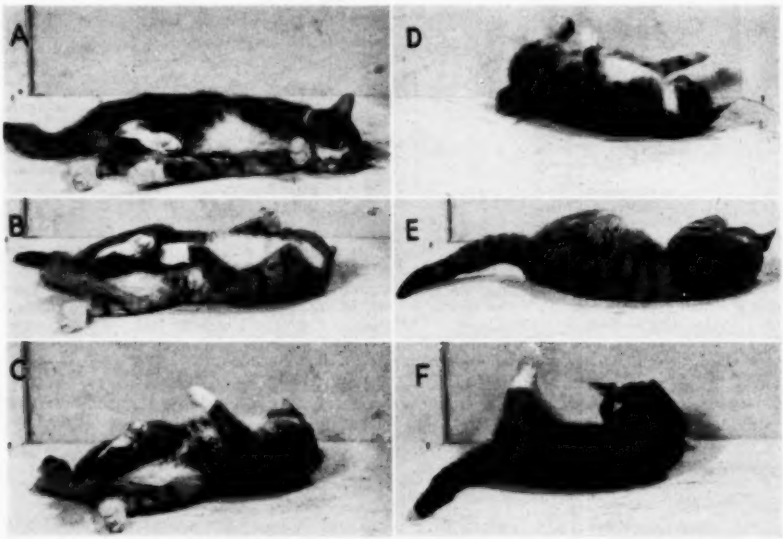

Fig. 3.—Rolling to the left in a cat after left semidecerebellation with involvement of the vestibular nucleus. This rolling was produced regularly by injections of pentylenetetrazol. Identical rolling occurred in the opposite direction when the bulbar nuclei were intact.

A shows typical posture of the cats similar to that seen immediately after the operation. After recovery this posture was reproduced by injections of pentylenetetrazol or of acetylcholine.

destruction of, or damage to, the ipsilateral bulbar structures (Fig. 1). Animals with semicerebellectomy, one-sided destruction of cerebellar nuclei, and unilateral lesions of the flocculonodular lobe in which no injury to the bulbar structures could be detected histologically constitute the second group. The third group includes animals with lesions in the cortex of half of the corpus cerebelli without involvement of the underlying cerebellar nuclei, the flocculonodular lobe, or the bulbar structures.

Semicerebellectomy with Involvement of Ipsilateral Vestibular Nuclei.—Four cats had excison of the left half of the cerebellum with a concomitant lesion of the ipsilateral vestibular nuclei. Immediately after this operation, the cats lay on the side of the cerebellar ablation, and when suspended in the air they curved to the side of operation. The animals were excited and active and frequently circled toward

Distribution of Forced Movements in Cats with Various Cerebellar Lesions During Chemically Induced Convulsions

Type of Lesion	Convulsant Drug	Amount, Mg./Kg.	No. of Animals Used	No. of Convulsions Observed	Direction of Forced Movements in Convulsions: Falling, Left (Same Side)	Falling, Right (Opposite Side)	Rolling, Left (Same Side)	Rolling, Right (Opposite Side)
Normal cats	Pentylenetetrazol	6-14	8	35	14	18	2	1
Semidecerebellate cats (left-sided ablation with extension of lesion into ipsilateral vestibular nuclei)	Pentylenetetrazol	6-10	4	17	10	0	7	0
	Acetylcholine	0.05-0.15		17	16	0	1	0
Cats with lesions of left cerebellar nuclei (without involvement of vestibular nuclei)	Pentylenetetrazol	6-14	12	74	14	42	1	17
	Acetylcholine	0.05-0.20		40	2	31	0	7
Cats with lesions of left flocculonodular lobe (without involvement of cerebellar or vestibular nuclei)	Pentylenetetrazol	6-14	4	31	5	17	0	9
	Acetylcholine	0.05-0.15		23	3	20	0	0
Cats with lesions of cortex of left corpus cerebelli (without involvement of cerebellar and vestibular nuclei or of flocculonodular lobe)	Pentylenetetrazol	8-14	5	21	10	10	0	1
	Acetylcholine	0.10-0.20		7	3	3	0	1

the side of the lesion by means of a grasping movement of the contralateral forepaw. One of these cats with the most extensive injury to the brain stem, including the vestibular nuclei (as later verified histologically), rolled spontaneously to the side of operation during the first four days after the operation. At the end of a month the animals were usually able to walk, although with considerable tremor and swaying. The forelimbs were held extended, but the hindlimbs were flexed so that the pelvis was kept close to the floor. Moving in this way, the cat tended to circle and to deviate toward the side of the lesion, and it frequently fell to the side of operation (Fig. 2 *A*). There was pronounced ataxia of the ipsilateral limbs. This pattern of behavior lasted during the whole period of observation (up to 15 months).

The injection of 6, 8, and 10 mg. of pentylenetetrazol per kilogram of body weight caused these cats to fall and to roll to the side of the lesion during their entire postoperative survival period (Fig. 3; Table). In comparison, the control group of animals without operation fell with almost equal frequency to either side. In the control group, also, rolling occurred in only 3 of the 35 pentylenetetrazol convulsions and was distributed at random to both sides, while in the semidecerebellate

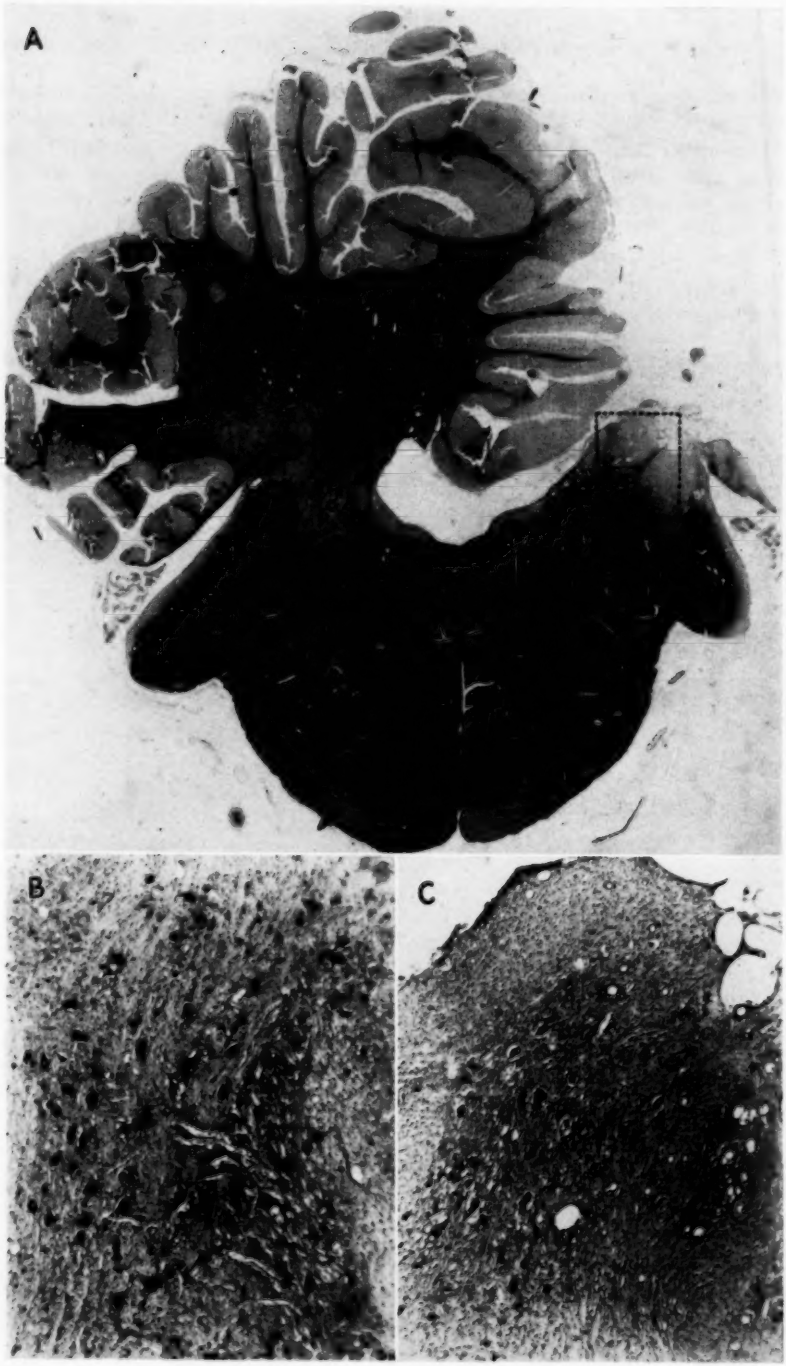

Figure 4

(See legend on opposite page)

cats rolling always took place to the side of operation and was observed in 7 of the 17 pentylenetetrazol convulsions. The intravenous administration of 0.05 to 0.15 mg. of acetylcholine chloride per kilogram of body weight caused the semidecerebellate cats to fall consistently to the side of the operation. The differencee between the pentylenetetrazol and the acetylcholine convulsions was the fact that in acetylcholine convulsions the great predominance of the tonic phase of the convulsion caused the animal usually to stop in its movement to one side in the posture acquired during the initial fall, whereas with pentylenetetrazol the movement was oftener continued into a roll. The same difference between pentylenetetrazol and acetylcholine convulsions was observed very clearly also in the next group of animals, in which the lesions were localized to the cerebellar nuclei or to the flocculonodular lobe.

Histologically, transverse sections of the cerebellum and brain stem showed that the left half of the cerebellum, including the left cerebellar nuclei and the left fastigiobulbar tract, was entirely excised, while the right half of the cerebellum remained intact (Fig. 4 *A*). In Figure 4 *B* and *C*, it can be seen that the cells of the left vestibular nuclei had been severely damaged by the ablation of the overlying half of the cerebellum and by subsequent scarification, while the right vestibular nuclei showed no structural changes.

Lesions of Left Cerebellar Nuclei and of Left Flocculonodular Lobe Without Involvement of Bulbar Structures.—In this group, of 16 cats, 12 animals with lesions of the cerebellar nuclei are grouped together with 4 cats in which the flocculonodular lobe was excised because they presented a common picture during the period of recovery from the operation and exhibited the same pattern of convulsions when they were given injections of acetylcholine and with pentylenetetrazol.

The cats with an excision of the left cerebellar nuclei without extension of the lesion to the underlying bulbar structures, or with a lesion restricted to the left flocculonodular lobe, were typically subdued, and crouched as though frightened on the day after the operation. They also leaned consistently to the side opposite the lesion during the first week (Fig. 2 *B*). When these animals could be induced to move around, four or five days after the operation, they exhibited a generalized tremor, as well as ataxia of the limbs on the same side as the operation. Recovery after this type of operation occurred much more rapidly than after a lesion which involved the vestibular nuclei, and after three weeks to one month the animals behaved very normally and showed no residual effects of the operation.

The injection of 6 to 14 mg. of pentylenetetrazol and 0.05 to 0.20 mg. of acetylcholine chloride per kilogram of body weight caused the animals to fall and to roll to the side opposite the lesion in a great majority of the convulsions (Table). This falling and rolling to the side opposite that of operation during chemically

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EXPLANATION OF FIGURE 4

Fig. 4.—Cross section of the cerebellum and brain stem of cat shown in Figure 2 *A*, killed 379 days after left semidecerebellation with involvement of the vestibular nucleus on the side of the ablation.

A, extent of ablation of the left half of the cerebellum (Weil stain); *B* and *C*, cells of the right and left vestibular nuclei respectively, as outlined by the squares in *A* (cresyl violet).

Note the diminished number of nerve cells in the left vestibular nucleus, indicating involvement of the bulbar structures in the cerebellar ablation.

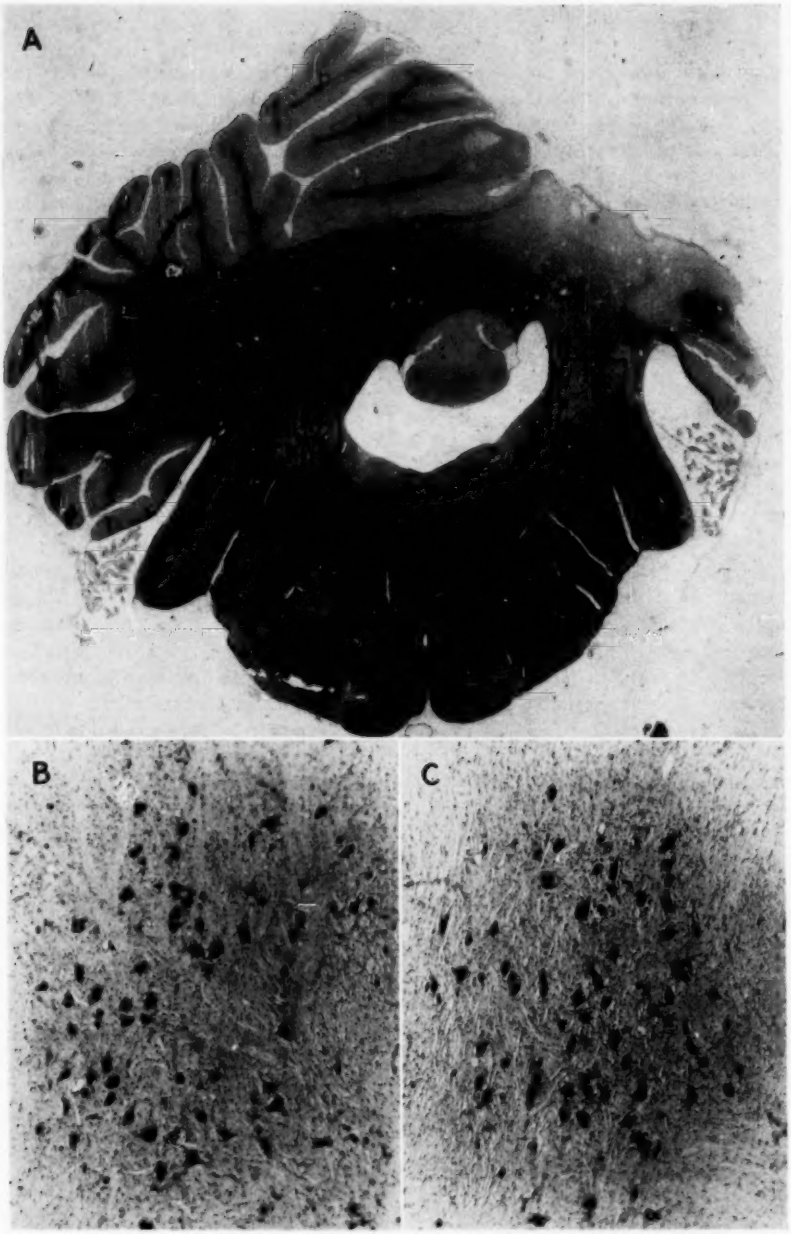

Fig. 5.—Cross section of the cerebellum and brain stem of the cat shown in Figure 2*B*, killed 259 days after left semidecerebellation, showing complete removal of the cerebellar nuclei but absence of any extension of the lesion to the bulbar structures.

A, extent of ablation of the left half of the cerebellum (Weil stain); *B* and *C*, cells of the right and left vestibular nuclei respectively, as outlined by the squares in *A* (cresyl violet).

Note the complete degeneration of the fastigiobulbar tract on the left side in *A*, but the equal number of nerve cells in the right and left vestibular nuclei, as seen in *B* and *C*.

induced convulsions was in direct contrast to the forced movements toward the same side as the lesion in semidecerebellate cats with a concomitant lesion of the ipsilateral vestibular nuclei during similar convulsions. In view of the fact that no other region of the cerebellar cortex produced asymmetrical convulsions, the lesions of the flocculonodular lobe are of particular interest. As shown in the Table, of 31 convulsions induced by means of injections of pentylenetetrazol into four animals with such lesions, the cats fell in 17 and rolled in 9 to the side away from the lesion, falling only five times, and never rolling, to the side of operation. Of 23 convulsions induced by injections of acetylcholine, the cats fell in 20 to the side away from the operation and in only three toward the side of the lesion.

It is interesting that two cats with ablation of the cortex of the left half of the nodulus and uvula only fell regularly to the side opposite the lesion when receiving injections of pentylenetetrazol but never completed the rolling movement which was so characteristic of one-sided lesions of the whole flocculonodular lobe.

Histologically, in all the cats with lesions of the cerebellar nuclei, a transverse section of the cerebellum and brain stem showed complete degeneration of the left fastigiobulbar tract from the region of the destroyed left medial cerebellar nuclei to the left vestibular nuclei, in the medulla. The right fastigiobulbar tract was uninjured (Fig. 5 *A*). Examination of the cells of the vestibular nuclei in sections stained with cresyl violet showed that the lesion did not extend to underlying bulbar structures and that the vestibular nuclei were intact on both sides (Fig. 5 *B* and *C*). The sections also showed that in the two cats with flocculonodular ablations the cortex of the posterior part of the left half of the nodulus and the lower part of the uvula on the left side of the midline and the left flocculus had been removed. The cortex of the posterior part of the left half of the nodulus and the lower left part of the uvula only had been ablated in the other two animals.

Lesions of Cortex of Left Corpus Cerebelli Without Involvement of Underlying Cerebellar Nuclei or Deeper Structures.—The cats with different cortical lesions of the corpus cerebelli exhibited a transient tremor and moderate ataxia in the ipsilateral limbs during the first postoperative month, but there was no disturbance of their equilibrium. Subsequent examination of transverse sections of the cerebellum and brain stem showed that neither the underlying cerebellar nuclei nor any other deeper structure had been injured. The injections of 8 to 14 mg. of pentylenetetrazol and 0.10 to 0.20 mg. of acetylcholine chloride per kilogram of body weight caused these cats to fall with equal frequency to the side of operation and to the side away from the operation during the ensuing convulsions (Table). Rolling occurred in only two convulsions, and on the whole there was no detectable asymmetry during the convulsions.

Combined Cerebral and Cerebellar Lesions.—Combined lesions of the cerebellum and the cerebrum were produced in five cats. In these animals the effect of the cerebral lesion usually predominated over that of the cerebellar lesion as regards the direction of falling and rolling which occurred during a convulsion, except in the case in which the cerebellar lesions extended to the vestibular nuclei. In this case the vestibular lesion dominated the direction of the falling and rolling during the convulsions. When the left cerebellar nuclei were destroyed without involvement of the ipsilateral vestibular nuclei, so that the cat fell and rolled to the right during chemically induced convulsions, the subsequent removal of the right cerebral

hemisphere would reverse these features of the convulsion and would cause the animal to roll to the left. On the other hand, if the left vestibular nuclei was involved in the ablation of the left half of the cerebellum, so that the cat rolled to the left during a convulsion, the removal of the left cerebrum would not cause the animal to reverse the direction of its falling and rolling during subsequent convulsions.

COMMENT

From the results which have been presented, it can be seen that in chemically induced convulsions the extension of the lesion to the bulbar nuclei determined the direction of the falling and rolling in the semidecerebellate cats. Lesions which extended into the bulbar structures, particularly into the vestibular nuclei, caused the cats to fall and to roll to the same side as the lesion, while complete unilateral ablation of, or damage to, the cerebellar nuclei which did not extend into the bulbar structures caused the animals to fall and to roll away from the side of the lesion during chemically induced convulsions.

Decortication of various regions of the corpus cerebelli did not result in any asymmetry during the convulsion as long as the cerebellar nuclei were not damaged. The only cortical lesion which resulted in falling and rolling away from the side of the lesion during chemically induced convulsions was ablation of the flocculonodular lobe.

The results in sacrifice experiments which involve stimulation or ablation of various regions of the cerebellum are not strictly comparable to these results, because there was not complete recovery from the effects of the anesthesia and the operative procedure, because there was insufficient time for sensitization of the denervated neurones to appear, and because many of these observations were made on decerebrate animals. This procedure may affect the equilibrium of the mechanism which governs postural tone and thus lead to results not identical with those seen in intact animals. The delicacy of this mechanism can be inferred from the experiments of Moruzzi,[18] who showed that variations in the rate of electric stimulation applied to the anterior lobe of the cerebellum caused reversal from inhibition to facilitation of the decerebrate rigidity. Consequently, this discussion must be limited to observations on chronic animals, and the present findings may be compared advantageously, and are in general agreement, with many earlier observations on the behavior of chronic animals after various cerebellar ablations. Thus, Ferrier[19] showed that cauterization of one lateral lobe of the cerebellum caused the animals to roll away from the side of the lesion. This was subsequently confirmed by Luciani,[20] who also noted that, contrary to the previous observation, after removal of half the cerebellum a dog rolled to the side of the lesion. It was further shown by Fulton, Liddell, and Rioch[21] that unilateral lesions of the vestibular nuclei in cats produced

18. Moruzzi, G.: Effects at Different Frequencies of Cerebellar Stimulation upon Postural Tonus and Myotatic Reflexes, Electroencephalog. & Clin. Neurophysiol. **2**:463-469, 1950.

19. Ferrier, D.: The Functions of the Brain, London, Smith, Elder & Co., 1886, p. 186.

20. Luciani, L.: Human Physiology: Vol. 3, Muscular and Nervous Systems, translated by F. A. Welby and edited by Gordon Holmes, London, Macmillan & Co., Ltd., 1915, pp. 430-485.

21. Fulton, J. F.; Liddell, E. G. T., and Rioch, D.: Influence of Unilateral Destruction of the Vestibular Nuclei upon Posture and the Knee-Jerk, Brain **53**:327-343, 1930.

forced rolling movements to the side of operation. Camis [22] suggested that the rolling movements to the same side as the lesion after the removal of half the cerebellum were actually due to a concomitant lesion of the lateral vestibular nuclei rather than to the cerebellar excision. This suggestion receives support from the observations of Ferraro and Barrera,[23] who showed that a unilateral cerebellar lesion involving the vestibular nuclei caused monkeys to fall to the side of the operation, while a lesion restricted to the one fastigiobulbar tract (supramedullary juxtarestiform body) caused the animals to deviate to the side opposite the lesion. Finally, Dow [24] found that monkeys with a unilateral ablation of the cortex of the nodulus and lower half of the uvula of the cerebellum also fell and deviated to the side opposite the lesion.

On the anatomical side, it was observed by Allen [25] that the fastigiobulbar fibers terminated in the ipsilateral vestibular nuclei and the dorsal reticular formation of the medulla and entered the medial longitudinal fasciculus. Dow [26] noted that direct fibers from the cortex of the nodulus and uvula also ended in the ipsilateral vestibular nuclei. Thus, the common feature in all the animals exhibiting forced movements to the side opposite the lesion, both spontaneously and during chemically induced convulsions, was the fact that fibers passing directly to the vestibular nuclei on the same side as the lesion were sectioned, while animals which deviated to the same side as the cerebellar lesions had some direct damage of the vestibular nuclei on that side.

Two facts help in the interpretation of these observations. One is that destruction of a labyrinth causes the animal to deviate to the side of the lesion, while stimulation of the semicircular canals on one side causes the animal to undergo a forced movement around its longitudinal axis toward the opposite side (McNally and Tait [27]). Thus, a lesion in the vestibular nuclei on one side incurred during the ablation of the overlying half of the cerebellum would cause the animal to deviate, to fall, and to roll to the side of operation because of the predominance of the intact contralateral vestibular nuclei. An injection of stimulating agents, such as acetylcholine and pentylenetetrazol, would further aggravate this tendency. On the other hand, a partial isolation of the vestibular nuclei on one side by means of severance of their afferent connections should, according to the "law of denervation" formu-

22. Camis, M.: Physiology of the Vestibular Apparatus, translated by R. S. Creed, Oxford, England, The Clarendon Press, 1930, p. 260.

23. Ferraro, A., and Barrera, S. E.: Effects of Lesions of the Juxtarestiform Body (I. A. K. Bundle) in Macacus Rhesus Monkeys, Arch. Neurol. & Psychiat. **35**:13-29, 1936.

24. Dow, R. S.: Effect of Lesions in the Vestibular Part of the Cerebellum in Primates, Arch. Neurol. & Psychiat. **40**:500-520, 1938.

25. Allen, W. F.: Distribution of the Fibers Originating from the Different Basal Cerebellar Nuclei, J. Comp. Neurol. **36**:399-439, 1924.

26. Dow, R. S.: The Fiber Connections of the Posterior Parts of the Cerebellum in the Rat and Cat, J. Comp. Neurol. **63**:527-548, 1936; Efferent Connections of the Flocculonodular Lobe in Macaca Mulata, ibid. **68**:297-305, 1938.

27. McNally, W. J., and Tait, J.: Some Results of Section of Particular Nerve Branches to the Ampullae of the Four Vertical Semicircular Canals of the Frog, Quart. J. Exper. Physiol. **23**:147-196, 1933.

lated by Cannon,[28] cause the development of hyperexcitability of the neurones in the vestibular nuclei on that side. In the case of the destruction of a labyrinth such a sensitization of the vestibular nuclei was shown to occur by Spiegel and Demetriades.[29] In those of our cats in which the cerebellar ablations resulted in degeneration of direct fiber connections to the vestibular nuclei, pentylenetetrazol or acetylcholine caused the animals to deviate, to fall, and to roll away from the side of the lesion during a convulsion. It seems reasonable to assume that injections of these chemical agents led to the overaction of the sensitized vestibular neurones, thus causing the characteristic asymmetry. The rolling of the cats to the opposite side after unilateral cauterization of the cerebellar cortex seen by Ferrier [19] and by Luciani [20] can be accounted for in this manner. The cauterization would conceivably establish a focus of irritation in the fastigial nucleus and in the flocculonodular lobe or its fiber projections, thus causing a greater facilitation of the vestibular nuclei on the side of the cauterization.

The sensitization of the vestibular nuclei, and possibly of other bulbar structures, became marked only after ablation of the cerebellar nuclei or after destruction of the flocculonodular lobe. The unilateral ablation of other areas of the cerebellar cortex which do not send direct fibers to the bulbar nuclear masses did not produce any disturbance of equilibrium, either after operation or during chemically induced convulsions. This absence of any observable disturbances of equilibrium in lesions of the cortex of the corpus cerebelli agrees with the findings of Carrea and Mettler,[30] who made equilibratory dysfunction one of their criteria in dividing the cerebellum into "vestibular" and "non-vestibular" regions. Jansen and Brodal [31] pointed out that fibers from the cortex of the cerebellum projected directly to the underlying cerebellar nuclei. Thus, for instance, exteroceptive and proprioceptive impulses reaching the vermis of the "non-vestibular" cerebellum might be relayed through the medial cerebellar nuclei to the underlying vestibular nuclei and thereby influence the equilibratory adaptations of the animal. However, since these fibers did not pass directly to the vestibular nuclei, the cells of the vestibular nuclei would not become sensitized by lesions of the "non-vestibular" vermis.

It is interesting to note that ablations of other regions of the cerebellar cortex which are known to influence motor activity [32] did not show any visible change in the pattern of convulsions. This is particularly noteworthy in view of the recent findings of Snider and Eldred,[33] who have shown the existence of very wide con-

28. Cannon, W. B.: A Law of Denervation, Am. J. M. Sc. **198**:737-750, 1939. Cannon, W. B., and Rosenbleuth, A.: Supersensitivity of Denervated Structures, New York, The Macmillan Company, 1949, pp. 185-186.

29. Spiegel, E. A., and Demetriades, T. D.: Die zentrale Kompensation des Labyrinthverlustes, Arch. ges. Physiol. **210**:215-222, 1925.

30. Carrea, R. M. E., and Mettler, F. A.: Physiologic Consequences Following Extensive Removals of the Cerebellar Cortex and Deep Cerebellar Nuclei and Effect of Secondary Cerebral Ablations in the Primate, J. Comp. Neurol. **87**:169-288, 1947.

31. Jansen, J., and Brodal, A.: Experimental Studies on the Intrinsic Fibers of the Cerebellum: II. The Cortico-Nuclear Projection, J. Comp. Neurol. **73**:267-321, 1940.

32. Sherrington.[7] Miller and Banting.[8] Miller and Laughton.[9] Clark.[11] Nulsen and others.[12] Snider and Magoun.[13] Snider and others.[14] Moruzzi.[15] Chambers and Sprague.[16]

33. Snider, R. S., and Eldred, E.: Cerebro-Cerebellar Relationship in the Monkey, J. Neurophysiol. **15**:27-40, 1952.

nections between the cerebellar cortex and various sensory cortical areas of the cerebral hemispheres. It seems that a direct denervation of the vestibular nuclei, and possibly other nuclei of the reticular formation, is the essential feature leading to motor asymmetry during the convulsion. This denervation and ensuing sensitization occur on destruction of cerebellar nuclei and on damage to the flocculonodular lobe, but do not take place in cortical lesions of the cerebellum, as all the fiber connections coming from the cortex of the corpus cerebelli terminate in the cerebellar nuclei and the effect of penultimate denervation on the bulbar structures is not great enough to be registered in that manner. How much of the asymmetry seen during the convulsions was due to a vestibular component and how much of it was due to other structures to which cerebellar nuclei connections project is impossible to estimate, but it is surprising that there was no detectable difference in the pattern of convulsions between the animals in which the flocculonodular lobe alone was removed and in those in which all the cerebellar nuclei were destroyed. Thus, it seems that at least the basic component in the present experiment was of a vestibular nature.

Forced movements of cats with unilateral cerebral ablation to the side opposite the lesion during pentylenetetrazol and acetylcholine convulsions are similar to those seen with unilateral cerebellar lesions and dominate the latter. The source of these forced movements following cerebral lesions may possibly also be a partial isolation and subsequent sensitization of cells of the ipsilateral bulbar nuclei. On the other hand, Drake and Stavraky [3d] have shown that spinal neurones become sensitized by the unilateral ablation of the cerebral motor cortex. It may be that overactivity of these neurones led the animals to fall and to roll to one side during convulsions induced after unilateral cortical lesions.

SUMMARY AND CONCLUSIONS

In a series of 25 cats aseptic removal of various regions of the cerebellum was carried out, and after complete recovery of the animals convulsions were induced by means of intravenous injections of pentylenetetrazol (metrazol®) or acetylcholine.

1. Removal of half the cerebellum, with a histologically verified extension of the lesions into the ipsilateral bulbar nuclei, caused the cats to lie on the side of the lesion and sometimes to roll to that side. Compensation progressed, until one year after the operation tremor and ipsilateral ataxia were the only outstanding residual symptoms. At that time injections of pentylenetetrazol or of acetylcholine reproduced during the convulsions the original syndrome of cerebellar removal, the animal falling, rolling, staggering, and circling to the side operated on.

2. After ablation of the cerebellar nuclei with and without decortication of half the cerebellum, and in the absence of any extension of the lesions to the bulbar nuclei, the cats were ataxic on the side of the lesion but leaned and staggered to the opposite side for one to three weeks. After complete recovery from the leaning and staggering, pentylenetetrazol and acetylcholine caused in these animals convulsions, during which the cats fell, rolled, staggered, and circled to the side opposite the cerebellar lesion.

3. Ablation of the flocculonodular lobe (partial or complete) gave results essentially similar to those seen after the ablation of the cerebellar nuclei. On the other hand, various cortical lesions of the corpus cerebelli did not influence the direction of the falling and rolling of the animals during the convulsions.

It is believed that the forced movements of the cats to the same side as the lesion following a semicerebellectomy in which the ipsilateral bulbar structures were damaged was due to the activity of the uninjured, and therefore relatively predominant, contralateral vestibular nucleus, and possibly other brain-stem nuclei. The deviation of the animals to the side opposite the ablation following unilateral lesions of the cerebellar nuclei or of the flocculonodular lobe in which no detectable damage to the bulbar structures was incurred is interpreted as being due to a partial isolation and consequent sensitization of the ipsilateral vestibular nucleus, and possibly other bulbar nuclei. Similarly, it is suggested that the absence of any equilibratory dysfunction during convulsive manifestations following lesions of the cortex of the corpus cerebelli was due to the lack of direct fiber connections to the vestibular or other bulbar nuclei from this region of the cerebellum and consequent absence of any change in the sensitivity of these nuclei to convulsant agents after such ablation of the cerebellar cortex.

ASCENDING FIBERS IN PYRAMIDAL TRACT OF CAT

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IN THE neurological literature of recent years much debate has been devoted to the pyramidal tract. Publications from the fields of anatomy, physiology, and clinical neurology have contributed greatly to improve the understanding of this nerve pathway and its function, but there are still deplorable gaps in knowledge of this tract. One of these gaps concerns the question of the exact origin of the fibers of the pyramidal tract.[1]

Häggqvist [2] and Lassek [3] have shown that removal of Area 4 of the cerebral cortex in monkeys leaves intact a considerable proportion of fibers in the medullary pyramid, and that consequently the origin of the pyramidal fibers must be more widespread. Contributions to the tract from the parietal cortex have been demonstrated, and from the premotor cortex by some authors (cited by Lassek and Evans [4] and Tower [5]), but even after precentral and extensive parietal ablations more than 50% of the fibers of the medullary pyramid are preserved (Lassek [3]). Fibers from the occipital and temporal lobes appear not yet to have been demonstrated.

Most studies of the pyramidal tract have been made on monkeys and man. While subcortical contributions to the tract (fibers from the lenticular nucleus) have been demonstrated in the rabbit by Swank,[6] such fibers appear to be sparse in man, if present at all, according to the findings of Lassek and Evans,[4] who after a practically complete human hemispherectomy found only a very small number of preserved fibers in the corresponding pyramid. These authors did not venture any suggestions as to the origin of the preserved fibers running lengthwise in the pyramid.

From the Anatomical Institute, University of Oslo.

1. When used in this communication, the term "pyramidal tract" is taken to comprise all fibers running together in the pyramids of the medulla, regardless of their site of origin or termination.

2. Häggqvist, G.: Faseranalytische Studien über die Pyramidenbahn, Acta psychiat. et neurol. **12**:457-466, 1937.

3. Lassek, A. M.: The Pyramidal Tract: Effect of Pre- and Postcentral Cortical Lesions on the Fiber Components of the Pyramids in Monkey, J. Nerv. & Ment. Dis. **95**:721-729, 1942.

4. Lassek, A. M., and Evans, J. P.: Human Pyramidal Tract: XII. Effect of Hemispherectomies on Fiber Components of Pyramids, J. Comp. Neurol. **83**:113-119, 1945.

5. Tower, S. S.: The Pyramidal Tract, in Bucy, P. C., Editor: The Precentral Motor Cortex, Illinois Monographs in Medical Sciences, Vol. IV, Urbana, Ill., University of Illinois Press, 1944, pp. 149-172.

6. Swank, R. L.: The Pyramidal Tract: Experimental Study of Corticospinal and Other Components in the Rabbit, Arch. Neurol. & Psychiat. **36**:530-541, 1936.

The possibility that there may be some ascending fibers among the vast majority of clearly descending ones in the pyramid appears not yet to have been seriously considered, the current conception of the pyramidal tract being that it is purely an efferent, descending pathway. In her review of 1944, Tower [5] states emphatically: "All that can be said with certainty is that all fibers running lengthwise in the medullary pyramids are descending fibers." Her statement is based on the observation that after section of the pyramidal tract at the level of the trapezoid body in a monkey no preserved fibers running lengthwise were seen 32 months after the operation.

It was surprising, therefore, to discover in an experimental cat material prepared for other purposes that there are, in fact, ascending fibers in the pyramid and that such fibers take origin in the spinal cord. Since there is some intermingling of the fibers of the pyramid and those of the medial lemniscus in the cat, as recently emphasized by Glees, Liddell, and Phillips,[7] our attention was secondarily directed also to the possibility suggested by these authors, i. e., that fibers from the nuclei of the dorsal column (Goll and Burdach) might join the pyramidal tract during its course rostral to the medulla. This proved to be the case, as will be shown below, where a brief account of our findings is given.

MATERIAL AND METHODS

The observations to be reported were made in an experimental material prepared for study of the course and distribution of ascending fibers from the spinal cord to centers of the brain stem in the cat. Under pentobarbital anesthesia, the animals were subjected to various lesions of the spinal cord or of the dorsal-column nuclei and were kept alive for three to six days. They were then killed by exsanguination while under chloroform or pentobarbital anesthesia and the brain and spinal cord immediately dissected free. The part of the spinal cord or medulla containing the lesion was fixed in 96% alcohol, subsequently embedded in paraffin, and sectioned serially. The sections were stained with thionine to make possible an accurate determination of the extent of the lesion. The brain, including the brain stem and the cerebellum, was fixed by immersion in formalin or formol-saline solution. After fixation, the medulla and pons were isolated and cut as frozen sections, usually in the horizontal plane. The blocks were cut serially at 15 μ and the sections collected in groups of 15 consecutive ones. Of each group, one or two sections were selected for silver staining for the demonstration of degenerating fibers, degenerating terminal fibers, and boutons. For this purpose, the modified Bielschowsky method of Glees [8] was employed. The brains of other cats, treated in the same manner, served as normal controls.

OBSERVATIONS

Our attention was directed to the presence of ascending fibers in the pyramid when we were studying the spinal afferent fibers to the pontine nuclei in the cat. Contrary to current teaching, it was observed that there are in the spinal cord ascending fibers which establish synaptical contact with cells of the pontine nuclei. The results of this study are published elsewhere (Walberg and Brodal [9]). In all cases in which terminal degeneration was present in the pontine nuclei, degenerating

7. Glees, P.; Liddell, E. G. T., and Phillips, C. G.: Der Verlauf der medialen Schleife im Hirnstamm der Katze, Ztschr. Zellforsch. u. mikr. Anat. **35**:487-494, 1951.

8. Glees, P.: Terminal Degeneration Within the Central Nervous System as Studied by a New Silver Method, J. Neuropath. & Exper. Neurol. **5**:54-59, 1946.

9. Walberg, F., and Brodal, A.: Spinopontine Fibers in the Cat, J. Comp. Neurol., to be published.

nerve fibers were seen between the fibers of the pyramids and could be followed through the pons into the cerebral peduncles. Their number depended on the site of the lesion. The course of these ascending degenerating fibers will be described as it appeared in the following representative case.

CAT Sp. C. L. 18.—Killed six days after the lesion was placed (Figs. 1, 6, and 7*A*).

By means of a knife, a lesion was made in the left dorsal horn, extending from the second to the sixth cervical segment. Serial transverse sections of the cervical part of the spinal cord showed that, in addition to the dorsal horn, the dorsal half of the left lateral funiculus had been severely injured and that there was some involvement of the left cuneate fasciculus (Fig. 1).

In silver sections of the pons, typical terminal degeneration of fibers and boutons was seen on both sides (Fig. 6*A*). The degeneration was similar on the right and left sides of the pons; it is indicated by dots in the diagrams of Figure 1, the density of the dots giving an approximate impression of the intensity of terminal degeneration.

In both medullary pyramids a certain number of fibers were in the process of degeneration (Sections *2*, *3*, and *5*, Fig. 1, and Fig. 6*B*). Their number was moderate, but they presented the characteristic picture of degeneration. Rostrally, these fibers could be traced into the pyramidal fiber bundles of the pons (Fig. 6*C*) and, farther, into the peduncles (Fig. 6*D*). In the pons some fibers bent rostrolaterally or rostromedially and were lost between the pontine cells. These were taken to be fibers destined to terminate in the pontine gray matter. In addition, some very fine degenerating fibers were seen to enter the pontine gray matter. These were interpreted as being collaterals of ascending degenerating fibers (Fig. 6*E*). In the fiber bundles of the medial lemniscus ascending in the trapezoid body, scattered degenerating fibers were seen in the area dorsal to the pyramid. Their number was so small that they were not indicated in the drawings of Figure 1.

When followed caudally and in more dorsal sections, the degenerating fibers in the pyramid were seen to enter it from the pyramidal decussation (Sections *8* and *13*, Fig. 1). Some crossed the midline in the decussation; others pursued a straight ascending course. The majority of degenerating fibers in the decussation were seen to stream into it, intermingled with the fibers of the lateral corticospinal tract on both sides (Section *13*, Figs. 1 and 6*F*). A minor proportion was derived from the medialmost part of the ventral funiculus of the cord, from the zone allotted to the ventral corticospinal tract (Sections *5* and *8*, Figs. 1 and 7*A*), Their number was here clearly smaller on the right side than on the left.

While the diameter of nerve fibers cannot be exactly determined when they are degenerating, a certain indication of their original size when normal may, nevertheless, be obtained. It appeared that the majority of degenerating fibers observed belonged to the medium-sized type, but there were also some which must certainly have been very thin when normal. Occasionally a degenerating fiber was seen which appeared to have been rather heavy (Figs. 6*B* to *D*). The area of the pyramid and its rostral and caudal continuations were easily recognized in these silver preparations, and it differed clearly in appearance from the medial lemniscus. While the lemniscus appeared to be composed chiefly of medium-sized fibers of a rather uniform diameter, the pyramidal tract was seen to contain fibers of very different calibers. (This observation is in conformity with fiber analysis of these tracts published by other authors.)

Observations essentially similar to those in this case were made in other cases, in which the dorsal one-half or one-third of the lateral funiculus had been transected at high cervical levels. A diagram of the lesion in one such case is shown in Figure 2 (Cat Sp. C. L. 13). The only difference between this case and the case shown in Figure 1 is the very slight degeneration in the ventral funiculus of the spinal cord in the latter case. Degeneration in the lateral corticospinal tract, the pyramidal decussation, the pyramids, and the peduncles was practically as intense as in Cat Sp. C. L. 18 (Fig. 1).

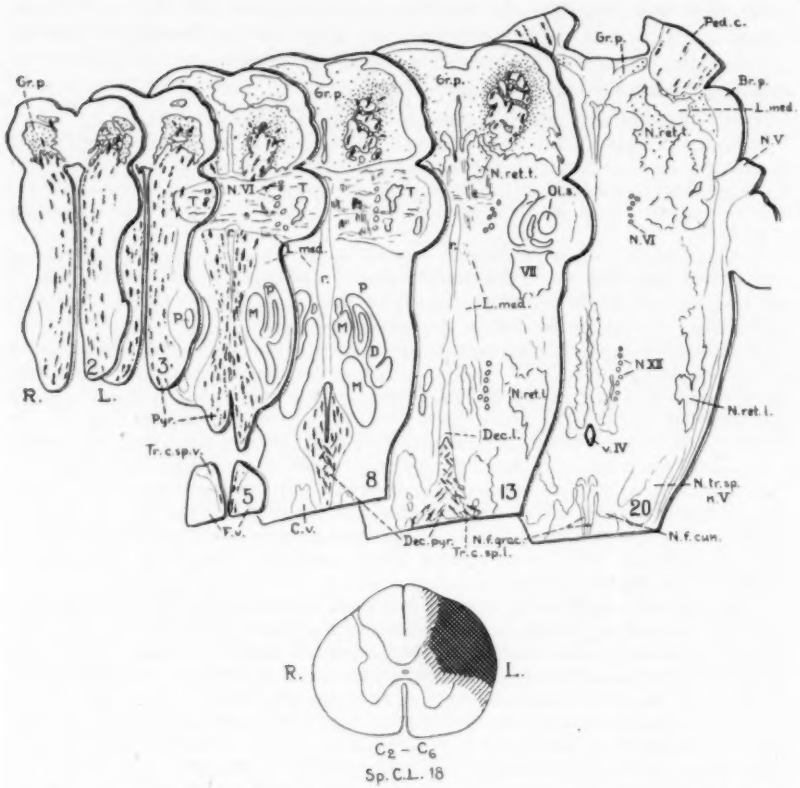

Fig. 1.—Diagram of the findings in Cat. Sp. C. L. 18. Below: Diagram of the lesion; totally destroyed areas are cross-hatched; partially damaged areas are single-hatched. Above: Drawings (outlines made by means of a projection apparatus) of representative horizontal sections through the brain stem. The number of each drawing refers to the group of 15 consecutive sections to which the reproduced section belongs and serves to indicate the relative intervals. Degenerating fibers are shown as wavy, broken lines; the distribution and relative intensity of terminal degeneration in the pontine gray matter are indicated by dots. Degenerating fibers can be followed from the lateral and ventral corticospinal tracts into the pyramids and cerebral peduncles. The fibers degenerating in the dorsal and lateral funiculi (apart from those in the pyramidal tract) as a consequence of the lesion are not shown.

Abbreviations employed in Figures 1 to 5 are as follows: *Br. p.*, brachium pontis; *C.v.*, ventral horn of spinal cord; *D*, dorsal accessory olivary nucleus; *Dec. l.*, decussation of medial lemniscus; *Dec. pyr.*, decussation of pyramid; *F.v.*, ventral funiculus of spinal cord; *Gr. p.*, pontine gray matter; *L.*, left; *Lat.*, lateral; *L. med.*, medial lemniscus; *M*, medial accessory olivary nucleus; *Med.*, medial; *N. cerv. lat.*, lateral cervical nucleus; *N.f. cun.*, nucleus of cuneate fasciculus (Burdach); *N.f. grac.*, nucleus of gracile fasciculus (Goll); *N. ret. l.*, lateral reticular nucleus (nucleus funiculi anterioris); *N. ret. t.*, nucleus reticularis tegmenti (Bechterew); *N. tr. sp. n. V.*, nucleus of spinal tract of trigeminal nerve; *N. V*, trigeminal nerve; *N VI*, root fibers of abducent nerve; *N VII*, root fibers of facial nerve; *N XII*, root fibers of hypoglossal nerve; *Ol. s.*, superior olivary nucleus; *P*, principal olivary nucleus (inferior olivary nucleus); *Ped. c.*, cerebral peduncle; *Pyr.*, pyramid; *R.*, right; *r.*, raphe; *T*, trapezoid body; *Tr. c. sp. l.*, lateral corticospinal tract; *Tr. c. sp. v.*, ventral corticospinal tract; *v. IV*, fourth ventricle; *VII*, nucleus of facial nerve; *X*, dorsal motor nucleus of vagus nerve; *XII*, nucleus of hypoglossal nerve.

After lesions had been similarly placed at the midthoracic and lumbar levels, there was convincing degeneration of the same fiber bundles as those in cases with cervical lesions (Fig. 2). However, the more caudal the lesion, the more moderate the number of degenerating fibers. But even with lesions as low as the fifth lumbar segment (Cat Sp. C. L. 11) degenerating fibers were clearly to be seen in the silver sections through the pyramids and peduncles, and the terminal degeneration in the pontine nuclei was unequivocal (Walberg and Brodal[9]).

In all cases mentioned so far the lesion involved the lateral as well as the dorsal funiculus, and these experiments do not permit conclusions as to which of these funiculi is utilized by the ascending fibers in the pyramid. Other cases demonstrated that lesions restricted to the dorsal funiculus were not followed by degeneration of ascending fibers in the pyramid. Thus, there was no degeneration in Cat R. 159, in which both dorsal funiculi had been almost completely transected at the level of the second cervical segment (Fig. 3). The negative findings in the pyramid, pons, and peduncles in Cat R. 81, in which the dorsal roots of the sixth, seventh, and eighth

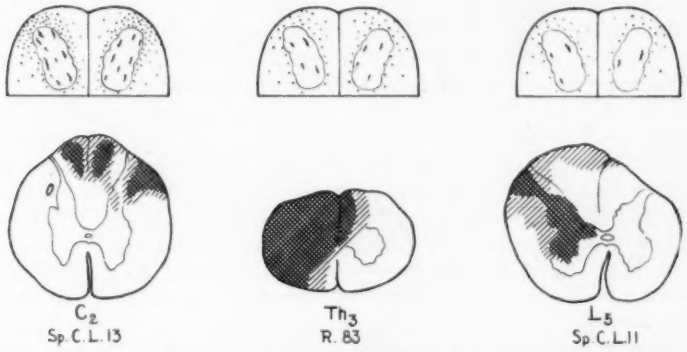

Fig. 2.—Diagrams of the findings in experiments with lesions at various levels of the spinal cord (symbols as in Figure 1). The pontine gray matter and the pyramidal bundles penetrating it are shown as simplified diagrams above the drawings of the lesions. The markings in these diagrams serve to give an impression of the relative intensity of degeneration in the different cases. The more rostral the lesion, the more intense is the degeneration.

cervical spinal nerves had been transected proximal to their ganglia, substantiate this result and make clear that the ascending fibers in the pyramid are not primary sensory neurons but must have their perikarya in the gray matter of the cord.

More precise information on the place of the ascending pyramidal fibers within the spinal cord is obtained from cases in which the lesion involves various parts of the lateral funiculus. While lesions restricted to the ventral part of the lateral funiculus (Cat R. 113, Fig. 3) were not followed by any degeneration in the pyramids or the pons, there was some degeneration when the lesion of the dorsal half of the lateral funiculus approached the dorsal horn (Cat R. 103, Fig. 3) and there was considerable degeneration when a lesion affected the dorsomedial part of the lateral funiculus (Cat Sp. C. L. 23, Fig. 3).

A comparison of these cases, as well as others not mentioned or illustrated, makes clear that the area of the lateral funiculus which, when destroyed, yields degenerating

ascending fibers in the pyramid coincides very closely with the place allotted to the lateral corticospinal tract. This area, as determined by McKibben and Wheelis,[10] is outlined by a broken line in the diagram for Cat R. 113, in Figure 3. Furthermore, lesions sparing this area but affecting the ventral funiculus at high cervical levels (Cat Sp. C. L. 26, Fig. 3) were also followed by some, but relatively moderate, degeneration of ascending fibers in the pyramids and by terminal degeneration in the pons. The degeneration was equal on the two sides, and degenerating fibers were seen to ascend in the ventral funiculi, while there was no degeneration in the area of the lateral corticospinal tract.

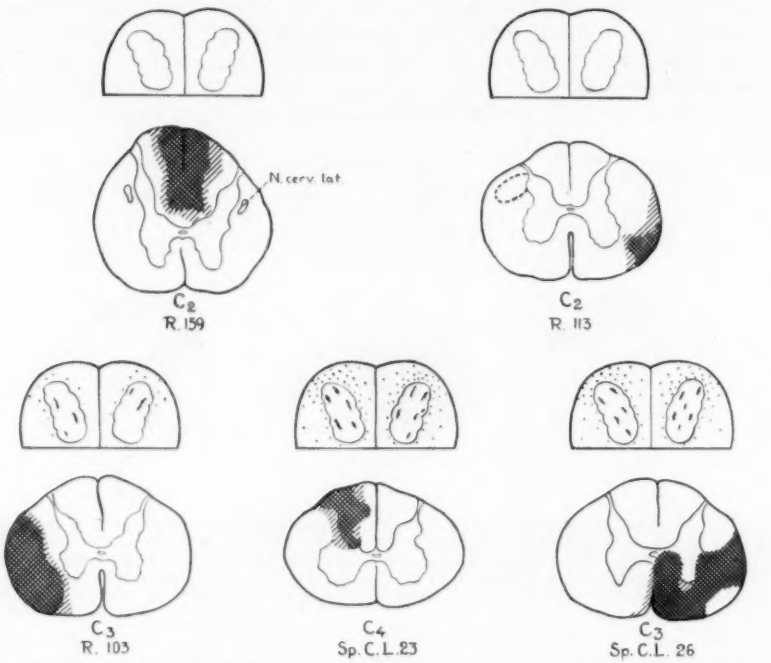

Fig. 3.—Diagrams of the findings in experiments involving various areas of the cord at high cervical levels (symbols and abbreviations as in Figure 1). In the drawing of the cord of Cat R. 113 the interrupted line indicates the area occupied by the lateral corticospinal tract, according to McKibben and Wheelis.[10] Only when this area or the medial part of the ventral funiculis is damaged does degeneration occur in the pyramids and pons.

The experiments reported show that the ascending fibers demonstrated in the pyramid and following this structure rostrally into the cerebral peduncles are derived from the spinal cord, even from levels caudal to the fifth lumbar. The increasing number of degenerating fibers as the lesion is placed at successively more rostral levels shows that such fibers take origin also from higher levels of the cord. The

10. McKibben, P. S., and Wheelis, D. R.: Experiments on the Motor Cortex of the Cat, J. Comp. Neurol. **56**:373-389, 1932.

cervical contribution appears to be relatively most important, since there is a pronounced difference between the results of high cervical and those of midthoracic lesions. The majority of the fibers ascend intermingled with those of the lateral corticospinal tract; a smaller proportion, in the ventral funiculus, between the fibers of the ventral corticospinal tract. In the pyramidal decussation a certain proportion of the fibers cross to the other side, with the consequence that the degeneration of ascending fibers, as well as of terminal fibers and boutons in the pons, is always practically identical on the two sides. The presence of ascending degenerating fibers in the right ventral funiculus in Cat Sp. C. L. 18 (Fig. 1), with a lesion on the left side, may be explained only by the extensive lesion of the gray matter in that animal, indicating that fibers originating in one dorsal horn ascend on both sides of the cord. Some of these crossing fibers also ascend in the contralateral (right) lateral corticospinal tract, since there was also degeneration in this tract where it entered the pyramidal decussation (Section 13, Fig. 1). However, even with pure transections of the lateral corticospinal tract, with only slight involvement of the gray matter (corresponding to the cut), fibers were seen to cross from the undamaged side to the side of the lesion in the pyramidal decussation. It appears therefore that a certain number of ascending fibers of one lateral corticospinal tract may cross to the tract of the opposite side, but where this takes place cannot be decided from the material available. The same conclusion applies to the fibers ascending in the ventral corticospinal tract, since degeneration here is also always bilateral.

Since the demonstration of ascending fibers in the pyramids is contrary to current conceptions, and since the silver methods have been criticized for being too delicate, we found it of interest to make a control experiment with the Marchi method. In one animal (Cat Sp. C. L. 25) a left hemisection of the cord was made at the sixth cervical level (Fig. 4). Eight days later the brain was fixed intravitally by perfusion with formalin. After removal of the brain, the right half of the brain stem was prepared as usual for silver sections, while the left half was treated according to the Marchi method for frozen sections as elaborated by Glees.[11] In the silver-impregnated sections the findings were as in the other cases described, that is, degeneration of ascending fibers in the pyramid, peduncle, and pontine gray matter. The medial part of the left half of the brain stem was sectioned sagittally; the rest horizontally. In the parasagittal sections stained by the Marchi method there was conspicuous degeneration of ascending fibers in the pyramid (Figs. 4 and *7B*). The degenerating fibers could be followed rostrally through the pons into the cerebral peduncles. In addition, there were fibers which passed dorsal to the olive and joined the fibers of the medial lemniscus. Rostrally, these fibers gradually were displaced ventrally and appeared to join the fibers ascending in the pyramidal bundles between the pontine gray nuclei. The degenerating fibers in the lemniscus did not belong to those taking origin in the nuclei of the dorsal funiculus. These were seen in the sections, but while their afferent fibers were degenerated on account of the lesion of the left dorsal funiculus, no degenerating fibers were seen to leave them. The caliber of the degenerating fibers visible in the Marchi preparations varied considerably (Fig. *7B*).

The findings in this case thus substantiate the results obtained with the silver method and, in addition, demonstrate that many of the ascending pyramidal fibers are

11. Glees, P.: The Marchi Reaction: Its Use on Frozen Sections and Its Time Limit, Brain **66**:229-232, 1943.

myelinated. It is likely that if the lesion had been at the second cervical level, the degeneration would have been even more pronounced. Since degenerating fibers show up more conspicuously in Marchi preparations than in silver sections because of the greater contrast with normal fibers, a better idea can be obtained of their number. It is clear that the number of ascending fibers in the pyramid of the cat, although not very great, is quite remarkable. Exact quantitative data cannot be gained from the material at hand, but as a rough approximation we would suggest that the ascending fibers do not represent more than one twenty-fifth of the entire number of pyramidal fibers, quite possibly less. The presence of some degenerating fibers which leave the pyramid to join the medial lemniscus for a certain distance is more apparent in the parasagittal Marchi sections than in the horizontal silver sections, in which these fibers are only slightly conspicuous.

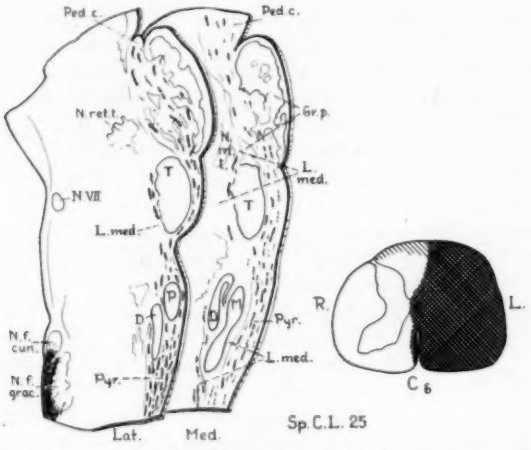

Fig. 4.—Drawings (outlines made by means of a projection apparatus) of two parasagittal sections through the brain stem of Cat Sp. C. L. 25, showing the occurrence and distribution of ascending degenerating fibers in Marchi sections following an extensive lesion of the spinal cord at the sixth cervical level (abbreviations as in Figure 1). Degenerating fibers ascend in the pyramid and cerebral peduncles, some also intermingling with the fibers of the medial lemniscus. See also Figure 7*B*.

In view of the presence of such aberrant pyramidal fibers to the medial lemniscus, it is of particular interest to observe that, on the other hand, a certain proportion of true lemniscal fibers leave this tract and continue rostrally in the pyramids and peduncles. The following case is illustrative.

Cat Sp. C. L. 17.—Killed six days after placement of the lesion (Figs. 5 and 7*C* and *D*). A lesion was made in the right cuneate nucleus by means of a small scalpel. Serial Nissl-stained sections through the lesion showed that the rostral half of the right cuneate nucleus had been destroyed and that probably some of the fibers from its caudal half had been injured. The gracile nucleus was intact, but the lesion encroached slightly on the dorsal motor nucleus of the right vagus nerve and the medialmost part of the medial vestibular nucleus.

In horizontal silver-stained sections of the brain stem, the fibers from the right cuneate nucleus, degenerating as a consequence of its lesion, were clearly to be followed, except for the first part of their course, which was in the Nissl-stained block. The degenerating fibers

from the right cuneate nucleus made their appearance lateral, medial, and somewhat caudal to the right medial accessory olivary nucleus (Sections *6* and *9*, Fig. 5) and passed in a mediorostral direction toward the raphe, to enter the decussation of the medial lemniscus. Some of the fibers penetrated the medial accessory olivary nucleus. Rostral to the decussation numerous degenerating fibers ascended in the medial lemniscus on the left side, between the raphe and the inferior olivary nucleus (Fig. 7*C*) and could be followed rostrally to the trapezoid body as a conspicuous bundle. Here they were split into several minor bundles by the transversely running fibers of the trapezoid body. In more dorsal sections the degenerating fibers occupied chiefly the medial two-thirds of the medial lemniscus and were seen to pass

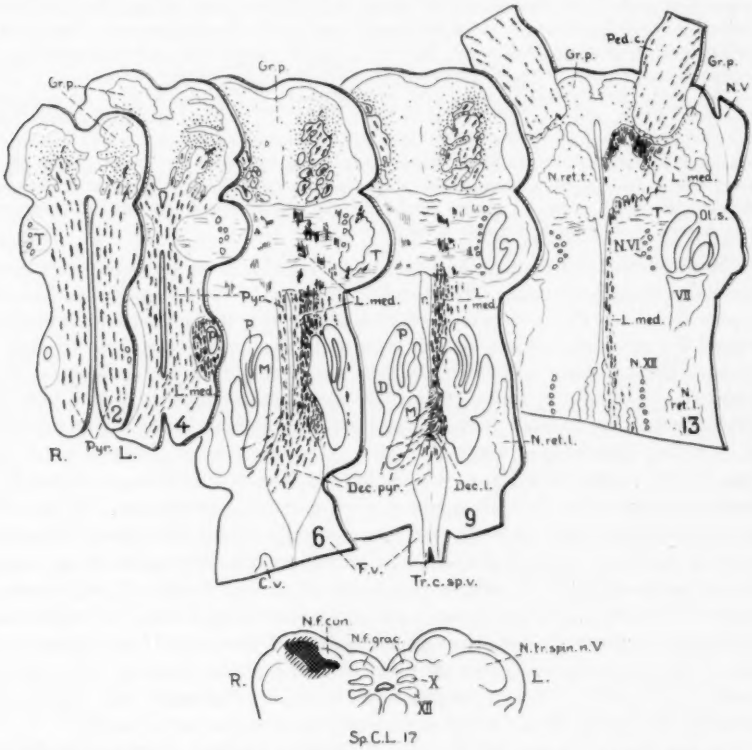

Fig. 5.—Diagram of the findings in Cat Sp. C. L. 17 (symbols and abbreviations as in Figure 1). The bulk of fibers degenerating as a consequence of a lesion of the right cuneate nucleus are seen to cross to the other side to ascend in the medial lemniscus, but some of them make their way into both pyramids at the level at which the pyramidal decussation is in contact with the decussation of the medial lemniscus. They can be followed into both cerebral peduncles.

ventral to the nucleus reticularis tegmenti of Bechterew. The fibers of the lemniscus were there separated from the more ventrally situated pyramidal fascicles in the pons by small strands of the pontine gray only (Section *13*, Fig. 5). In ventral sections (*4* and *6*, Fig. 5) some fibers of the degenerating lemniscus were seen also lateral and ventral to the left inferior olivary nucleus, and some also took their course through it. There was no degeneration of the fibers of the right lemniscus.

In addition to the clear-cut unilateral degeneration of the medial lemniscus, there was bilateral degeneration of fibers in the cerebral peduncles and in the pyramids (Figs. 5 and 7 *D*). This degeneration was practically equal on the two sides. It was far less intense than in the medial lemniscus (Figs. 5 and 7 *C*), but more pronounced than in cases with lesions of the spinal cord (Cat Sp. C. L. 18, Fig. 1, for example). When traced caudally, the degenerating fibers in the pyramids were seen to enter them from the pyramidal decussation (Sections *6* and *9*, Fig. 5). Some of the degenerating fibers in the pyramidal decussation could be seen to be derived from bundles of lemniscus fibers approaching the midline (Sections *6* and *9*, Fig. *5*). Some of them crossed to the other side; some ascended in the pyramid on the same side. That these fibers are actually lemniscus fibers taking off into the pyramids, and not fibers from the spinal cord ascending in the pyramids, is substantiated by the absence of degenerating fibers in the ventrocaudal part of the pyramidal decussation and in its continuation in the ventral funiculus of the cord (*tr. c.sp. v.* in Section *9*, Fig. 5), where the pyramidal fibers form a narrow zone, differing clearly in appearance from the rest of the ventral funiculus.

The fibers showing degeneration in the pyramids were of differing calibers; most of them appeared to have been of medium size in the normal state. Where the degenerating fibers passed between the nuclei of the pontine gray matter, some of them bent laterally or medially, apparently to terminate in the pons. Other fibers appeared to give off collaterals. However, there appeared not to be a great reduction of fibers in the pons, since there was still ample degeneration in the peduncles above (Section *13*, Fig. 5). Terminal degeneration in the pons was present, as indicated by the dots in Figure 5.

In three other cases with lesions of the nuclei of the dorsal funiculus, corresponding observations were made. Thus, in Cat B. St. L. 24 the left gracile nucleus had been destroyed. The lesion extended ventrally beyond the central canal and interrupted the medialmost fibers of both lemnisci, i. e., those coming from the gracile nuclei. These degenerating fibers could be seen to ascend chiefly laterally, in both lemnisci. Ventrally the lesion reached the pyramidal decussation, which had suffered a just visible minute injury. In both pyramids and peduncles a certain number of ascending degenerating fibers were seen. They were not as abundant as in the case just described (Cat Sp. C. L. 17, Fig. 5), but clearly more numerous than could be explained by the trifling injury of the pyramidal decussation. The intensity of terminal degeneration in the pontine nuclei corresponded to the degree of degeneration of ascending pyramidal fibers. In two other cases the nuclei of the dorsal funiculi were damaged, in addition to a lesion of the spinal tract of the trigeminal nerve. Whether the latter lesion may have contributed to the degeneration of fibers found in the medial lemniscus cannot be decided, but in both cases degenerating fibers from the lemniscus entered the pyramids and could be traced rostrally into the cerebral peduncles. Terminal degeneration in the pontine nuclei was present, its intensity being proportional to the degeneration of fibers in the pyramids.

Although the lesions in the last three cases were not ideal, the four experiments described leave no doubt that some fibers of the medial lemniscus leave this tract to enter the pyramid on each side and follow the course of the pyramidal fibers in a rostral direction. Like the ascending pyramidal fibers derived directly from the spinal cord, those from the gracile and cuneate nuclei are distributed in approximately equal numbers to both pyramids and establish synaptical contact with cells of the same areas of the pontine nuclei, in part by means of collaterals, in part, it appears, by fibers terminating in the pontine gray nuclei. It appears that the contribution from the cuneate nucleus is considerably more abundant than that from the gracile nucleus. The parallelism of the two contingents of ascending fibers in the pyramid, therefore, is remarkably close. A comparison of the intensity of degener-

ation in the two types of experiments indicates that the contribution of ascending fibers to the pyramids from the nuclei of the dorsal funiculus is quantitatively more important than that from the spinal cord. Degeneration was, for example, more pronounced in Cat Sp. C. L. 17 (Fig. 5) than in Cat Sp. C. L. 18 (Fig. 1), although the lesion of the cuneate nucleus was not complete in the former, while at least the majority of ascending spinal fibers must have been damaged in the latter.

It having been established that there are ascending fibers in the pyramid and that these fibers continue rostrally in the peduncles, the question arises as to where these fibers terminate. The investigation of this problem actually involves the study of all nuclei situated along the course of the pyramidal-tract fibers on their way to the cerebral cortex, since it is possible that some or all of them terminate in subcortical nuclei, or at least give off collaterals. However, the question of paramount interest is whether some of the fibers ascend as far as to the cerebral cortex. We have not as yet studied extensively the question of the termination of the fibers, but have investigated only certain parts of the cerebral cortex. Blocks were removed from the cortex of both cerebral hemispheres in some of the cats showing ascending degenerating fibers in the pyramids. Selected sections from these blocks from the motor and sensory areas were stained with silver, as described previously, and a search was made for degenerating terminal fibers and boutons in the cortex. Alternate sections were stained by the Nissl method to facilitate identification of areas. Control sections were prepared from a normal animal.

In six experimental animals studied from this point of view, unequivocally degenerating fibers were observed in the subcortical white matter and in the areas of the cortex studied. The findings were practically identical in all cases. In the white matter degenerating fibers were seen to ascend in a straight or slightly oblique course, to enter the sixth layer of the cortex. Most of these fibers were rather fine, as can be seen from Figure 7*E*, taken from the right hemisphere of Cat Sp. C. L. 17 (Fig. 5), with a lesion of the right cuneate nucleus. Occasionally a somewhat coarser fiber was encountered. In the cortex itself fine degenerating fibers ascended almost perpendicularly to the surface, some, however, pursuing a slightly oblique course. They could be followed in decreasing numbers to the second layer, the external granular lamina; but in this layer all the degenerating fibers were very thin, and most of them tended to run parallel to the surface of the cortex, or a little obliquely. In the deeper layers of the cortex a certain number of very fine degenerating, presumably terminal, fibers occurred in addition to the ascending ones. Convincing terminal boutons have, however, been observed only very infrequently; neither were normal boutons common. In Figure 7*F* some degenerating fibers in the fifth layer of the right motor area in Cat Sp. C. L. 18 (compare Figure 1) are shown. The number of degenerating fibers is modest, but considerably greater than appears from the photomicrograph, since the depth of focus is very slight with the high magnification employed.

Degenerating fibers entering the cortex from the white matter, as well as degenerating fine fibers in the cortex itself, as described above, were observed in the anterior part of the posterior sigmoid gyrus and in the anterior sigmoid gyrus in areas in which giant pyramidal (Betz) cells were easily identified. These regions were taken to represent the motor area, or Area 4 of Brodmann's nomenclature. They were found within the area outlined on the basis of physiological experiments

as the motor area of the cat by Ward and Clark [12] and Garol.[13] Posterior to this region, an intermediate zone with less cortical degeneration was encountered but in the anterior parts of the lateral and middle suprasylvian gyri, posterior to the ansate sulcus, degeneration of cortical fibers was again conspicuous, and, indeed, more pronounced than in the motor area. According to Dusser de Barenne,[14] Winkler and Potter,[15] and Garol,[16] the areas presenting clear-cut degeneration would correspond approximately to Brodmann's Areas 5 and 7, and possibly to Areas 1 and 2 as well. In all cases degeneration was equal in the cerebral hemispheres, and more abundant in the "sensory" areas than in the motor; and it was more extensive with lesions of the nuclei of the dorsal funiculi than with lesions of the spinal cord.

Although, as far as is known, fibers of the spinothalamic tracts have not been convincingly traced to the cerebral cortex, the possibility that such fibers exist cannot be frankly denied. If such fibers exist, those degenerating in the cerebral cortex after lesions of the spinal cord might belong to the spinothalamic tracts. However, with lesions of the spinal cord leaving the spinothalamic tracts undamaged, as, for example, in Cat Sp. C. L. 13 (Fig. 2), degeneration in the cortex was, as in the other cases, investigated. Even if this observation does not exclude the existence of spinothalamic fibers reaching the cortex, it proves that at least a major proportion of the spinocortical fibers ascend in the pyramids. With regard to the cortical termination of fibers of the medial lemniscus, it cannot in the same way be settled that the cortical afferent fibers are only those ascending in the pyramids, since the fibers of the lemniscus proper are also affected. The fact that the cortical degeneration is equal in the two hemispheres when one cuneate nucleus is damaged, as is the degeneration in the pyramids, favors the assumption that at least some of the cortical afferent fibers ascend in the pyramids. The possibility, however, should be recalled that true lemniscus fibers may cross above the level of the peduncles, as has indeed been suggested by some authors.

We have reason to believe that a closer study may reveal that the ascending fibers of the pyramid are distributed to other areas of the cerebral cortex, in addition to those so far investigated. The possibility of a somatotopical mode of termination also remains to be more closely studied, as well as the question of what layers of the cortex form the exact terminal site of the pyramidal afferent fibers. These problems, however, must be left for future studies. At present we prefer not to commit ourselves beyond the statement that the ascending fibers of the pyramid reach the motor and sensory areas of the cerebral cortex, that they are evenly distributed to the two hemispheres also after unilateral lesions of the cord or of the nuclei of the dorsal funiculus, and that sensory areas appear to receive more ascending pyramidal fibers than does the motor area.

12. Ward, J. W., and Clark, S. L.: Specific Responses Elicited from Subdivisions of the Motor Cortex of the Cerebrum of the Cat, J. Comp. Neurol. **63**:49-64, 1935.

13. Garol, H.: The "Motor" Cortex of the Cat, J. Neuropath. & Exper. Neurol. **1**:139-145, 1942.

14. Dusser de Barenne, J. G.: Experimental Researches on Sensory Localization in the Cerebral Cortex, J. Exper. Physiol. **9**:355-390, 1916.

15. Winkler, C., and Potter, A.: An Anatomical Guide to Experimental Researches on the Cat's Brain, Amsterdam, W. Versluys, 1914.

16. Garol, H. W.: Functional Organization of the Sensory Cortex of the Cat, J. Neuropath. & Exper. Neurol. **1**:320-329, 1942.

COMMENT

Degeneration of Ascending Fibers.—The demonstration in this study of ascending fibers in the pyramid of the cat is opposed to current conceptions. Nevertheless, there can, in our opinion, be no doubt as to the correctness of the observations. The affected fibers present unequivocal degenerative changes (Figs. 6 and 7). That they are not artifacts or random spontaneously degenerated fibers is shown by the consistency with which they are observed when the areas of the lateral or ventral corticospinal tracts or the nuclei of the dorsal funiculi are damaged and their equally consistent absence with lesions restricted to other areas. Furthermore, the concomitant clear-cut terminal degeneration in the pontine nuclei in cases in which there are degenerating fibers in the pyramid, and the absence of degeneration in the other cases, also shows that these fibers are true degenerating fibers. Finally, their verification in Marchi preparations is important.

The question might be raised whether the degenerating fibers observed in the pyramids in our experiments are virtually ascending ones. May they not be descending corticospinal fibers presenting retrograde degeneration? This explanation, however, can be discarded. Quite apart from the fact that it would be strange if only a very small number of fibers would be affected by retrograde degeneration, one of Lassek's [17] studies is decisive. After interruption of the pyramidal tract at the first cervical segment in monkeys, the fibers of the pyramid presented no signs of degeneration above the lesion, even as late as 10 months after the operation. Similar observations were made in cats and rats, and other authors have reported corresponding observations also in man (see Lassek [17] for references). One of us (A. B.) [18] likewise failed to find evidence of retrograde degeneration in the fibers of the facial nerve, although after its section clear-cut retrograde changes were seen in the cells of its motor nucleus. This lack of retrograde degeneration of the central end of transected fibers seems to be a rather general phenomenon, and Lassek's work rules out the possibility that the degenerating fibers reported in the present study are in the process of retrograde degeneration.

It may seem strange that these fibers, as far as we know, have not been observed by previous authors. However, we believe that reasons for this may be found in the following facts: The number of ascending fibers is small; and, as far as can be seen, no studies of the pyramids after lesions of the spinal cord have been made on silver preparations in the acute stage of degeneration, at least not with sections in which the fibers are cut longitudinally. The latter point, however, is essential, since a small number of degenerating fibers will be difficult to identify in sections in which they are cut transversely. Although numerous authors in the course of time have studied the occurrence of ascending degenerating fibers of the cord in Marchi preparations, they appear not to have observed those ascending in the pyramid. It is probable that the reason, again, is the plane of the sections employed. All authors appear to have cut the brain stem transversely, and in such preparations the occurrence of osmophilic granules in the area of a fiber bundle cannot be taken as conclusive evidence of degenerating fibers. However, if longitudinal sections are used,

17. Lassek, A. M.: The Pyramidal Tract: A Study of Retrograde Degeneration in the Monkey, Arch. Neurol. & Psychiat. **48**:561-567, 1942.

18. Brodal, A.: Experimentelle Untersuchungen über retrograde Zellveränderungen in der unteren Olive nach Läsionen des Kleinhirns, Ztschr. ges. Neurol. u. Psychiat. **166**:646-704, 1939.

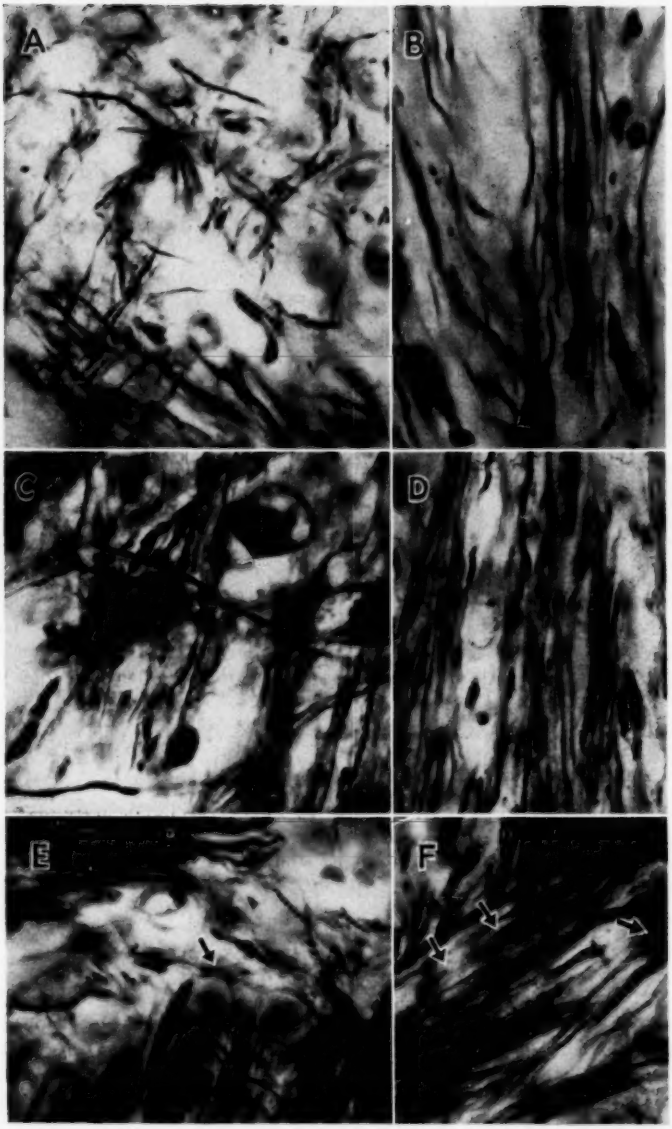

Fig. 6.—Untouched photomicrographs from the brain of Cat Sp. C. L. 18. Compare with Figure 1. × 900.

A, degenerating terminal and preterminal fibers and a few degenerating terminal boutons in the pontine gray matter. To the extreme left is a normal ring-like bouton. *B*, fine and relatively coarse degenerating ascending fibers in the left pyramid ventromedial to the inferior olivary nucleus. *C*, degenerating fine and relatively coarse ascending fibers in the pyramidal bundles of the pons, passing some pontine cells. *D*, degenerating ascending fibers of differing diameters in the cerebral peduncles. *E*, degenerating fine fibers (arrows), presumably collaterals, entering the pontine gray matter from the pyramidal fiber bundles (vertical). Some normal collaterals are seen below. *F*, degenerating fibers (arrows) coursing mediorostrally between the fibers of the lateral corticospinal tract to enter the pyramidal decussation.

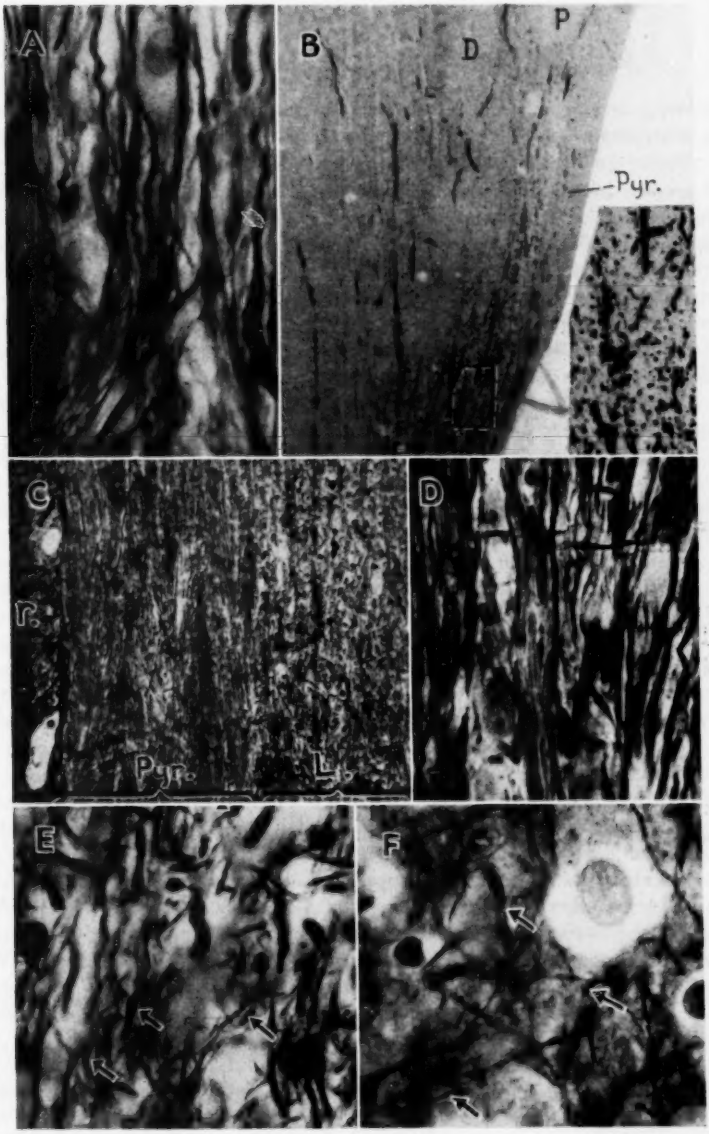

Fig. 7.—Untouched photomicrographs.

A, ascending degenerating fibers of the left ventral corticospinal tract of Cat. Sp. C. L. 18; × 900. *B*, paramedian section from the medulla of Cat Sp. C. L. 25, showing ascending degenerating fibers in the pyramid in a Marchi preparation 60 μ thick; × 23. A few fibers ascend in the medial lemniscus. Below to the right, area outlined with higher magnification (× 90), demonstrating the different calibers of myelinated fibers; *D*, dorsal accessory olivary nucleus; *P*, principal olivary nucleus; *Pyr.*, pyramid. Compare Figure 4.

C, ample degeneration of ascending fibers in the left medial lemniscus (*L*) and moderate number of degenerating fibers in the pyramid (*Pyr.*) of Cat Sp. C. L. 17, following a lesion of the nucleus of the right cuneate fasciculus. The raphe is indicated by *r*. × 90. Compare with Figure 5.

D, ascending degenerating fibers in the pyramid of Cat Sp. C. L. 17, shown in *C*; × 900.

E, degenerating subcortical fibers (arrows) entering the right motor cortex in Cat Sp. C. L. 17; × 900.

F, degenerating fibers (arrows) in layer V of the right motor cortex of Cat Sp. C. L. 18; × 900. In this photograph, and in the preceding photomicrographs taken with high magnification, only a minor proportion of the degenerating fibers actually present are in focus and can be seen.

these fibers, as has been shown, can easily be recognized in Marchi preparations. Since unmyelinated fibers are not shown in the Marchi preparations, silver methods are to be preferred for the study of this problem.

Ascending Fibers in the Corticospinal Tract.—It is interesting to note several points of resemblance between the fibers ascending from the spinal cord into the pyramid and the fibers descending in the corticospinal tract. For obvious reasons, referred to above, the diameters of the degenerating fibers cannot be determined, but it may be concluded from the findings that the ascending fibers in the pyramid are of very different calibers, there being very thin ones, a small proportion of thick ones, and a majority of medium-sized fibers. A similar wide range of fiber diameters is found in the pyramid as a whole (Häggqvist,[2] Lassek and Rasmussen,[19] Szentágothai-Schimert,[20] Brookhart and Morris[21]). With regard to their course, the ascending fibers, as has been shown, follow the fibers of the descending corticospinal tracts and occur intermingled with them. Most authors studying the pyramidal tract of the cat emphasize that the bulk of its fibers appear to terminate in the cervical part of the cord (McKibben and Wheelis,[10] Lassek,[22] Brookhart and Morris,[21] and others). It appears from our observations that, correspondingly, the majority of the ascending pyramidal fibers take origin in the cervical portion of the cord. With regard to the lowest levels of the cord to which the corticospinal fibers are distributed there is some disagreement. While some authors deny their presence below the midthoracic level in the cat, others (Brookhart and Morris,[21] Lassek,[22] Linowiecki,[23] Swank[24]) have traced the lateral corticospinal tract to lumbosacral levels. The demonstration in the present study that some ascending fibers in the pyramidal tract are derived from levels below the fifth lumbar is in accord with this. That some pyramidal fibers ascend in the ventral funiculus of the cord is of interest with regard to the dispute concerning the presence of a ventral corticospinal tract in the cat. While Rasmussen[25] did not find conclusive evidence of its presence, it has been described by Probst,[26] and more recently by Swank[24]; but this tract is apparently subject to some individual variations.

An essential point when one is comparing ascending and descending pyramidal fibers is their relation to the cerebral cortex. As has been stated, we have found unequivocal evidence that fibers ascending from the spinal cord in the pyramid and peduncles reach the motor, as well as the sensory, areas of the cerebral cortex. We

19. Lassek, A. M., and Rasmussen, G. L.: A Comparative Fiber and Numerical Analysis of the Pyramidal Tract, J. Comp. Neurol. **72**:417-428, 1940.

20. Szentágothai-Schimert, J.: Die Bedeutung des Faserkalibers und der Markscheidendicke im Zentralnervensystem, Ztschr. Anat. u. Entwcklngsgesch. **111**:201-223, 1941.

21. Brookhart, J. M., and Morris, R. E.: Antidromic Potential Recordings from the Bulbar Pyramid of the Cat, J. Neurophysiol. **11**:387-398, 1948.

22. Lassek, A. M.: The Pyramidal Tract: The Representation of the Lateral Corticospinal Component in the Spinal Cord of the Cat, J. Neuropath. & Exper. Neurol. **5**:72-76, 1946.

23. Linowiecki, A. J.: Comparative Anatomy of the Pyramidal Tract, J. Comp. Neurol. **24**:509-530, 1914.

24. Swank, R. L.: Aberrant Pyramidal Fascicles in the Cat, J. Comp. Neurol. **60**:355-359, 1934.

25. Rasmussen, A. T.: An Aberrant (Recurrent) Pyramidal Bundle in the Cat, J. Comp. Neurol. **51**:229-235, 1930.

26. Probst, M.: Zur Kenntnis der Pyramidenbahn (normale und abnormale Pyramidenbündel und Reizversuche der Kleinhirnrinde), Monatsschr. Psychiat. u. Neurol. **6**:91-113, 1899.

have not yet examined the entire cortex with regard to the terminal distribution of these fibers; but even if findings indicate that they terminate also outside the areas mentioned, the correspondence of the terminal areas with those giving origin to the corticospinal tract, outlined in the introduction to this paper, is worthy of attention. Of particular interest is the participation of sensory (parietal) cortex, which has been shown anatomically (Levin and Bradford,[27] Peele,[28] Gobbel and Liles,[29] and others), as well as electrophysiologically (Woolsey and Chang [30]), to be an important source of corticospinal fibers. It remains for further studies to elaborate more fully the correspondence between cortical areas for ascending and descending pyramidal fibers, but it appears that while the motor area (precentral in the monkey) is most important with regard to descending fibers, sensory (parietal) areas dominate as terminal areas for ascending fibers.

Just as the descending pyramidal fibers are known to give off collaterals to various nuclei during their course, so do the ascending fibers. We have studied more particularly the termination in the pontine nuclei. These appear to be supplied chiefly by means of collaterals from the ascending fibers, but, in addition, some of these appear to find their termination in the pontine nuclei. Although the number of such terminal fibers to the pons, and possibly to other nuclei, appears not to be very great, their occurrence tends to reduce somewhat the number of fibers reaching the cortex.

The chief difference between the ascending and the descending pyramidal fibers, apart from their opposite direction, appears to concern the proportion of crossed to uncrossed fibers. While the majority of the descending pyramidal fibers are by all authors found to cross to the opposite side of the cord, the ascending ones appear to be distributed approximately evenly to the two pyramids and to the cerebral hemispheres. The pyramidal decussation offers the possibility for this arrangement of the fibers. However, it appears that some fibers ascending for some distance in one lateral corticospinal tract cross in the cord to the tract of the opposite side, from which they may eventually again return via the decussation to the tract of their side of origin. We have not been able to determine how and where this crossing in the cord takes place. A similar arrangement, however, is found with regard to the fibers of the ventral funiculi, and it is of interest in this connection that Morin and O'Leary,[31] in Marchi material, have observed ascending fibers crossing from one ventral funiculus to the other along the ventral median fissure.

The remarkable similarities between the ascending and the descending fiber systems of the pyramidal tract in the cat may be borne in mind when these fibers are studied in other species. One might assume that as the descending pyramidal path-

27. Levin, P. M., and Bradford, F. K.: Exact Origin of the Cortico-Spinal Tract in the Monkey, J. Comp. Neurol. **68**:411-422, 1938.

28. Peele, T. L.: Cytoarchitecture of Individual Parietal Areas in the Monkey (Macaca Mulatta) and Distribution of the Efferent Fibers, J. Comp. Neurol. **77**:693-737, 1942.

29. Gobbel, W. G., Jr., and Liles, G. W.: Efferent Fibers of the Parietal Lobe of the Cat (Felis Domesticus), J. Neurophysiol. **8**:257-266, 1945.

30. Woolsey, C. N., and Chang, H. T.: Activation of the Cerebral Cortex by Antidromic Volleys in the Pyramidal Tract, A. Nerv. Res. & Ment. Dis., Proc. (1947) **27**:146-161, 1948.

31. Morin, F., and O'Leary, J. L.: Ascending Tracts of the Anterolateral White Column in Macaca Mulatta, abstracted, Anat. Rec. **106**:226, 1950.

way increases in bulk and importance in phylogenesis, so may the ascending fibers in the pyramid. If so, it may seem strange that Tower [5] did not find any preserved fibers in the pyramid of the monkey 32 months after section of the pyramids. However, her lesion was made at the trapezoid level, and it is possible that the lack of preserved fibers may have been a consequence of the level of the lesion. Either the intense processes of degeneration in the pyramid may indirectly have influenced also the ascending fibers or, more likely, the ascending fibers may have degenerated in a retrograde direction to a level below the pyramid, since it is possible that retrograde degeneration of central nerve fibers does not extend beyond the first collaterals central to the lesion. Whether the ascending fibers of the pyramid are devoid of collaterals during their course in the pyramid proper, as this explanation would indicate, is, however, not known.

The preserved fibers seen by Lassek and Evans [4] in the pyramid of the human brain after hemispherectomy may indicate that also in man ascending fibers are present in the pyramid, although other explanations may be suggested. It is clear that for a solution of the problem of ascending fibers in the pyramid an approach giving positive evidence of the presence of degenerating fibers is better suited than a study of the remaining normal fibers after degeneration of all descending ones; and the opportunity to study a suitable human brain would be of particular interest.

With regard to the cat, it is of interest to note that Lassek and Rasmussen [19] found preserved fibers in the area of the lateral corticospinal tracts after bilateral decortication. Although nothing definite can be said of the nature of these fibers, the assumption may be ventured that at least some of them represent ascending fibers demonstrated in the present study.

Pyramidal Fibers from Nuclei of Dorsal Funiculus.—Although some authors (Glees, Liddell, and Phillips [7]; Matzke [32]) have commented upon the intermingling of fibers of the medial lemniscus with those of the pyramid, the present study appears to be the first to demonstrate that fibers from the nuclei of the dorsal funiculus (Goll and Burdach) virtually join the pyramidal tract and ascend in this tract as far as the cerebral cortex. It is interesting to note some points of similarity between this ascending system and the ascending fibers in the lateral and ventral corticospinal tracts. Thus, fibers originating in the nucleus funiculi cuneati of one side are apparently evenly distributed to the two pyramids, in striking contrast to the unilateral course of the medial lemniscus. Furthermore, it is evident that the contribution from the cuneate nucleus exceeds that from the gracile nucleus, in close correspondence with the quantitative dominance of ascending fibers from the cervical portion of the cord in the spinocortical tracts. The fibers from the nuclei of the dorsal funiculi entering the pyramids appear to be of a more uniform caliber than those ascending in the cord, but their areas of termination within the cortex appear to coincide with those of the direct spinocortical fibers.

Functional Considerations.—The present study has demonstrated two new pathways transmitting impulses from the body and extremities to the cerebral cortex. Although quantitatively neither of them is impressive, it must be assumed that the impulses traversing them may influence the activity of certain areas of the cerebral

32. Matzke, H. A.: Course of Fibers Arising from the Nucleus Gracilis and Cuneatus of the Cat, J. Comp. Neurol. **94**:439-452, 1951.

cortex. The present, purely anatomical study does not give any direct information as to the functional role of these fiber systems, but a perusal of the literature gives hints which are of interest.

It appears likely that the two contingents of ascending fibers in the pyramid, in spite of their similarities, are not functionally entirely equivalent, but it is probable that they may be concerned with the transmission of different kinds of impulses. With regard to the spinocortical fibers, ascending directly from the cord to the cerebral cortex, certain findings indicate that they may be engaged in the transmission of cutaneous, presumably tactile, impulses. Thus, Berry, Karl, and Hinsey [33] recorded action potentials from the medulla following electrical stimulation of the saphenous nerve in cats, and from their Figure 4 it is seen that small potentials were obtained from both medullary pyramids. Although not decisive, this finding is of considerable interest, particularly in view of other indirect evidence which comes from studies on the lateral cervical nucleus. This is a hitherto neglected nucleus situated dorsally in the lateral funiculus of the first and second cervical segments of the cat's spinal cord (Fig. 3) and recently described by Rexed and Brodal.[34] Studying the spinal afferent fibers of this nucleus more closely, Brodal and Rexed [35] found that they ascend in the dorsalmost part of the lateral funiculus but that they do not belong to the dorsal spinocerebellar tract, since they take origin at levels of the cord above, as well as below, the column of Clarke. At the time of that study we did not consider the possibility that the scattered degenerating fibers found ventral to the area of the dorsal spinocerebellar tract in the cord and giving off collaterals to the lateral cervical nucleus might follow the course of the corticospinal tract in an ascending direction also in the brain stem. From the findings in the present study, it appears extremely likely that it is just these ascending pyramidal fibers which establish synaptical contact with the cells of the lateral cervical nucleus. The observation by Rexed and Strøm [36] that the lateral cervical nucleus is activated by stimulation of cutaneous nerves forms another support for the assumption that the ascending spinocortical fibers are concerned in the transmission of cutaneous, presumably tactile, sensations.

With regard to the pyramidal fibers to the cortex arising in the nuclei of the dorsal funiculus, the situation is apparently more complex. It is well known that in man the dorsal funiculi are essential for proprioception, and that two-point discrimination suffers when these funiculi are damaged. These nuclei thus appear not to be exclusively devoted to transmission of proprioceptive impulses, but it is possible that this is their chief function. The experimental studies of Sjøqvist and Weinstein [37] indicate at least that proprioceptive functions suffer when the medial lemniscus is transected, although a marked degree of recovery is possible.

33. Berry, C. M.; Karl, R. C., and Hinsey, J. C.: Course of Spinothalamic and Medial Lemniscus Pathways in Cat and Rhesus Monkey, J. Neurophysiol. **13**:149-156, 1950.

34. Rexed, B., and Brodal, A.: Nucleus Cervicalis Lateralis: A Spino-Cerebellar Relay Nucleus, J. Neurophysiol. **14**:399-407, 1951.

35. Brodal, A., and Rexed, B.: Spinal Afferents to the Lateral Cervical Nucleus in the Cat: An Experimental Study, J. Comp. Neurol., to be published.

36. Rexed, B., and Strøm, G.: Afferent Nervous Connexions of the Lateral Cervical Nucleus, Acta Physiol. scandinav. **25**:219-229, 1952.

37. Sjøqvist, O., and Weinstein, E. A.: Effect of Section of the Medial Lemniscus on Proprioceptive Functions in Chimpanzees and Monkeys, J. Neurophysiol. **5**:69-74, 1942.

So far, the assumptions of functional differences in the two systems ascending in the pyramid to reach the cortex are no more than conjectures, and it should, of course, not be forgotten that ultimately both systems appear to be distributed to the same parts of the cerebral cortex. Even so, this does not invalidate the assumption made, since it is apparent that the more one gets to know of the central nervous system, the more it becomes evident that sharp functional borders between fiber systems and areas are the exceptions, rather than the rule.

It is not possible at the present stage of knowledge to indicate more particularly what may be the functions of the two pathways described here. In view of their termination and course, it may be asked, however, whether they may be involved in postural reflexes having their center in the cerebral cortex. Considering the findings of Bard and Brooks,[38] it is tempting to suggest that particularly the direct spinocortical, presumably exteroceptive, fibers ascending in the pyramid may be in some way engaged in the tactile placing reactions, and the observations of Sjøqvist and Weinstein [37] point to the importance of the medial lemniscus for proprioceptive afferent fibers in the placing and hopping reactions. It would be futile to discuss this subject at length here, but in future studies on these reflexes the spinocortical pathway demonstrated here should be borne in mind.

Clinical Implications.—With the meager information on the possible functions of the pathways demonstrated in this study, particularly with the lack of information as to how well these systems are developed in man, nothing definite can be said about their clinical importance. However, the suggestion may be ventured that the spinocortical fibers ascending in the pyramid may represent the afferent link in the plantar reflex, and possibly in the abdominal reflexes. While the pyramidal tract is generally thought to be the efferent link in the plantar reflex, its afferent link appears not yet to have been determined. If the spinocortical fibers, as tentatively suggested above, mediate tactile impulses, this would fit in with their being the afferent link for the plantar reflex, in which the appropriate stimulus is, at least predominantly, tactile. The marked temporal and spatial summation of stimuli necessary to evoke the reflex would tally well with the assumption that even in man the fibers are scarcely abundant, even if, as shown by Kugelberg,[39] there is also in the afferent conduction from the sole of the foot to the cord a considerable delay on account of the participation of C-fibers, as well as of A-fibers. The evidence available at present is too scanty to justify a more detailed discussion of the suggestion made above, but it may be of interest to clinical neurologists when studying the normal and pathological plantar reflex. It should be recalled, however, that the doctrine of the role of the pyramidal tract in the plantar reflex may not be so securely established as is generally assumed, as shown by the studies of Mettler [40] in monkeys.

38. Bard, P., and Brooks, C. M.: Localized Cortical Control of Some Postural Reactions in the Cat and Rat Together with Evidence That Small Cortical Remnants May Function Normally, A. Res. Nerv. & Ment. Dis., Proc. (1932) **13**:107-157, 1934.

39. Kugelberg, E.: Demonstration of A and C Fibre Components in the Babinski Plantar Response and the Pathological Flexion Reflex, Brain **71**:304-319, 1948.

40. Mettler, F. A.: Physiologic Consequences and Anatomic Degenerations Following Lesions of the Primate Brain-Stem: Plantar and Patellar Reflexes, J. Comp. Neurol. **80**:69-148, 1944.

SUMMARY

Lesions were made in the spinal cord and in the nuclei of the dorsal funiculi in adult cats, and fibers degenerating as a consequence of the lesions were traced in horizontal silver-impregnated sections through the brain stem (Glees's method).

When the lesion of the spinal cord involves the areas of the lateral or ventral corticospinal tracts, degenerating fibers are consistently found in both pyramids and cerebral peduncles, and terminal degeneration is present in the pontine gray matter. Lesions restricted to other areas of the cord do not yield degeneration of this type. The ascending degenerating fibers follow the tracts mentioned in the rostral direction and are distributed equally to the two sides of the brain stem, even with unilateral lesions. While some fibers appear to cross in the cord, the majority cross to the other side in the pyramidal decussation. The ascending fibers in the pyramid take origin from levels of the cord as far caudal as the fifth lumbar, but the contribution from the cervical portion of the cord is quantitatively most impressive. The ascending fibers are of extremely variable caliber. Marchi sections show that many of them are myelinated. The number of ascending fibers cannot be exactly determined, but is estimated not to exceed one twenty-fifth of the total number of fibers in the pyramid.

After lesions of the nuclei of the dorsal funiculus, some of the degenerating fibers of the medial lemniscus enter the pyramidal decussation and follow both pyramids and cerebral peduncles in a rostral direction. Synaptical contact is established, chiefly by means of collaterals, with cells of the pontine gray nuclei in the same manner as do the fibers from the cord. The contribution from the cuneate nucleus appears to be greater than that from the gracile nucleus, and the fibers from the nuclei of the dorsal funiculi appear to be more numerous than those ascending from the spinal cord.

The degenerating fibers have been traced to certain areas of the cerebral cortex bilaterally. The motor and sensory areas have been studied more particularly. The sensory areas receive more of the ascending pyramidal fibers than the motor. The indications are that other cortical areas receive such fibers.

The organization of the direct spinocortical pathway demonstrated in this study presents striking similarities to that of the corticospinal tracts. Reasons are given that the ascending pyramidal fibers have not been observed previously. Their functional significance is briefly discussed. Certain reports in the literature favor the assumption that the spinocortical fibers mediate cutaneous, presumably tactile, impulses, while the pyramidal fibers from the nuclei of the dorsal funiculi chiefly serve the transmission of proprioceptive sensations. The suggestion is ventured that the new pathways demonstrated may be concerned in certain reflexes having their center in the cerebral cortex, such as the placing and hopping reactions in animals and the plantar reflex in man.

NOTE.—Since this paper was submitted for publication, electrophysiological studies performed in collaboration with Dr. B. Kaada have substantiated the findings reported. After electrical stimulation of cutaneous nerves distinct potentials can be led off from the pyramid, while smaller potentials follow stimulation of muscular nerves. Responses are largest from the contralateral upper extremity.

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ADRENOCORTICAL FUNCTION IN MULTIPLE SCLEROSIS

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THE ETIOLOGY of multiple sclerosis remains obscure. The extensive experimental studies pertaining to the role of hypersensitivity phenomena as a possible underlying mechanism in the development of demyelinating diseases in general, and of multiple sclerosis in particular, has recently been reviewed by Hurst.[1] Although the allergic causation of multiple sclerosis is far from being established, there is no doubt about the apparently spontaneous remissions and exacerbations which mark the course of this chronic, progressive disease. The tendency of multiple sclerosis to follow this particular clinical pattern leads one to investigate those nonspecific factors in human metabolism which are capable of altering tissue reaction. It is well established that an antibody-antigen reaction, as well as other types of inflammatory action, may be modified significantly by an alteration in the level of circulating adrenocortical steroids. It was only logical, therefore, that the status of spontaneous adrenocortical activity, as well as the effect of massive adrenocortical therapy, in a disease so prevalent and so disabling as multiple sclerosis should be investigated.

Glaser and associates [2] have reported the results of the short-term treatment of this disease with adrenocorticotropic hormone (corticotropin) and have described

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These studies were supported in part by grants from the National Multiple Sclerosis Society and the National Institutes of Health, United States Public Health Service.

1. Hurst, E. W.: Experimental Demyelination in Relation to Human and Animal Disease, Am. J. Med. **12**:547-560, 1952.

2. Glaser, G. H.; Merritt, H. H., and Trager, C. H.: Effect of Pituitary Adrenocorticotrophic Hormone (ACTH) on Multiple Sclerosis: A Preliminary Report, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 141.

beneficial results in certain instances. It appeared desirable to ascertain at this time whether adrenocortical function is normal, or nearly so, in patients with long-standing multiple sclerosis. If so, it can be anticipated that long-continued, high-dosage pharmacological effects of corticotropin or cortisone would be required to modify significantly the underlying pathological process. Such a therapeutic response could, in all probability, be obtained only at some expense to the organism, i. e., the development of one or more signs of adrenocortical overfunction (Cushing's syndrome). On the other hand, the demonstration of a significant degree of hypoadrenocortical function in patients with multiple sclerosis would suggest a study of the possible beneficial effect of substitution therapy. In this case therapy could be continued indefinitely at maintenance-hormone levels presumably without undesirable side-effects.

The present study was therefore undertaken to evaluate, by more precise methods, the status of adrenocortical activity in 10 patients presenting classic signs and symptoms of long-standing multiple sclerosis.

MATERIAL AND METHODS

All the patients studied were women, of ages ranging from 21 to 48, who were referred from the neurological outpatient clinics of the Peter Bent Brigham Hospital and the Massachusetts General Hospital.[3] The diagnosis was established on the basis of the usual clinical criteria and spinal fluid examination. The duration of the disease process, from the date of diagnosis, varied from 4 months to 12 years; thus, patients in all stages of multiple sclerosis were included. None of the subjects had undergone spontaneous remissions during a period of at least six months prior to the institution of study, and six of the patients were considered to be in a phase of acute exacerbation. All studies were carried out in the metabolic wards and laboratory of the Peter Bent Brigham Hospital. The methods utilized for eosinophile counts and urinary steroid determinations have previously been described.[4]

Adrenocortical function was assayed quantitatively in 10 women patients with multiple sclerosis by standard procedures previously developed in this laboratory.[5] The availability of corticotropin (ACTH) provides an opportunity to stimulate directly the adrenal cortex with its natural activator. This procedure has been demonstrated to produce an elevated adrenocortical secretion, with a resultant intensification of the metabolic and cellular reactions in which adrenocortical steroid hormones are known to participate.[6] Of the numerous physiological changes which follow upon a significant stimulation of the adrenal cortex with corticotropin, three have been selected as the basis of a specific clinical test of the capacity of the adrenal cortex to respond: (*a*) the decrease in the number of circulating eosinophiles, as determined by direct enumeration; (*b*) and (*c*) the rise in urinary excretion of 11-oxysteroids and 17-ketosteroids.

The decline in eosinophiles, although an indirect index, has been adequately demonstrated to reflect an increased output of adrenal corticoids of the 11, 17-oxysteroid prototype in conjunction with the administration of potent preparations of corticotropin. The increase of formal-

3. Dr. Ruth Stauffer, of the Neurological Clinic of the Peter Bent Brigham Hospital, and Dr. Raymond D. Adams, Neurologist, of the Massachusetts General Hospital, referred these patients.

4. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15-66, 1948.

5. (*a*) Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency, J. A. M. A. **137**:1005-1009, 1948. (*b*) Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Wilson, D. L.; Renold, A. E.; Fredrickson, D. S., and Jenkins, D.: Advances in the Diagnosis and Treatment of Adrenal Insufficiency, Am. J. Med. **10**:595-611, 1951.

6. Thorn, G. W., and Forsham, P. H.: Metabolic Changes in Man Following Adrenal and Pituitary Hormone Administration, in Recent Progress in Hormone Research, edited by G. Pincus, New York, Academic Press, 1949, Vol. 9, pp. 229-288.

dehydogenic-steroid (11-oxysteroid) excretion in the urine parallels adrenocortical activation, since the measurement is, in general, correlated with the biological activity of urinary steroids, whereas increased 17-ketosteroid excretion is, in all likelihood, the resultant of an increased output of adrenocortical androgens, as well as the metabolic conversion of 11, 17-oxysteroids to 17-ketosteroids. The use of these procedures in the measurement of adrenocortical reserve in normal subjects, patients with adrenocortical disease, and various nonendocrinological clinical disorders has been discussed elsewhere.[7]

Adrenocortical function in this study was estimated as follows:

1. *Level of Spontaneous Adrenocortical Activity.*—This was assessed by the determination of control 24-hour urinary excretion of formaldehydogenic steroids and 17-ketosteroids. The source of these substances in the female is considered to be largely, if not entirely, the adrenal cortex.

2. *Adrenocortical Capacity.*—(*a*) Four-Hour Corticotropin Test: The decline in the number of circulating eosinophiles which occurs four hours after a standard test dose (25 I. U.) of corticotropin administered intramuscularly is utilized in this procedure as the index of the capacity of the adrenal cortex to produce an immediate rise in the level of corticoid secretion.

(*b*) Forty-Eight Hour Intravenous Corticotropin Test of Adrenocortical Reserve: The decrease in eosinophiles and the rise in 24-hour excretion of formaldehydogenic steroids and 17-ketosteroids resulting from the intravenous infusion of a standard test dose (20 I. U.) of corticotropin during an 8-hour period on two successive days provide quantitative criteria of the ability of the adrenal cortex to respond to maximal stimulation.[8] This test is currently considered in this laboratory to be the procedure of choice in the final evaluation of adrenocortical secretory function.

(*c*) Prolonged Test of Adrenocortical Reserve: The ability of the adrenal cortex to sustain maximal secretory activity was measured by the administration over a 10-day period of daily eight-hour intravenous infusions of corticotropin. Such a stimulus undoubtedly tests not only the capacity of the gland to produce an elevated level of hormone synthesis and secretion, but also its ability to undergo and maintain structural hyperplasia in response to a prolonged specific stimulus. The indices of response utilized were the same as those described above.

OBSERVATIONS

Resting Adrenal Functions.—No clinical evidence of significant adrenocortical insufficiency was manifest in any patient. Resting levels of 17-ketosteroid excretion varied from 4.2 to 12.5 mg. per 24 hours, with a mean value of 7.3 mg. per 24 hours. The daily output of 17-ketosteroids in normal women ranges from 5.0 to 15.0 mg., with a mean of 10 mg. per day. The control values for formaldehydogenic-steroid excretion varied from 0.1 to 3.0 mg. per 24 hours, the normal range being 0.5 to 2.0 mg. per day. It is therefore evident that the control pattern of steroid excretion in this group of patients consists of (*a*) a moderate depression of 17-ketosteroid output, as reflected in the mean value for the entire group, and (*b*) an essentially normal excretion of formaldehydogenic steroids.

Four-Hour Corticotropin Test (Immediate Response to Corticotropin).—The four-hour corticotropin response as measured by the decline in circulating eosinophiles is summarized in Figure 1. A normal response to this test consists of an eosinophile fall of greater than 50%. The mean response of a fall of 66% elicited

7. Thorn, G. W., and others: ACTH Tests of Adrenal Cortical Function, to be published. Thorn and associates.[5b]

8. Renold, A. E.; Forsham, P. H.; Maisterrena, J., and Thorn, G. W.: Intravenously Administered ACTH, New England J. Med. **244**:796-798, 1951. Renold, A. E.; Jenkins, D.; Forsham, P. H., and Thorn, G. W.: The Use of Intravenous ACTH: A Study in Quantitative Adrenocortical Stimulation, J. Clin. Endocrinol. **12**:763-797, 1952.

in the patients with multiple sclerosis is obviously normal, and it may therefore be concluded that the capacity of these patients to produce an immediate increase in the secretion of 11, 17-oxysteroids resulting from corticotropin stimulation is, in all probability, intact.

Forty-Eight Hour Intravenous Corticotropin Test (Capacity of Adrenal Cortex to Respond to Maximum Stimulation).—The normal response to this procedure as determined in over 100 subjects without primary adrenal cortex disease (Table)

Normal Response to the Forty-Eight-Hour Intravenous Corticotropin (ACTH) Test in One Hundred Thirteen Control Subjects*

Response	First Day	Second Day
Mean eosinophile fall	97%	98%
Mean increase in 17-ketosteroid over control value, mg./24 hr.	4.4	8.7
Mean increase in formaldehydogenic steroids over control value, mg./24 hr.	5.0	7.0

* The test consists of intravenous administration of 20 I. U. of corticotropin in 500 cc. of isotonic sodium chloride solution or in 5% dextrose in distilled water on two consecutive days over an eight-hour period.

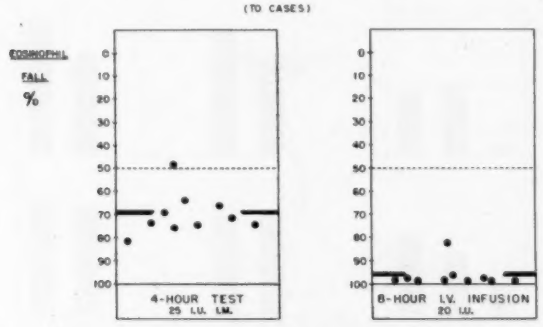

Fig. 1.—Changes in circulating eosinophiles after intramuscular and intravenous administration of corticotropin to patients with multiple sclerosis.

consists of (*a*) a mean eight-hour decrease in eosinophiles of 97%; (*b*) a mean 17-ketosteroid rise of 4.4 mg. per 24 hours on the first day and 8.7 mg. per 24 hours on the second day; (*c*) a mean increase in formaldehydogenic-steroid excretion of 5.0 and 7.0 mg. per 24 hours on the first and second days, respectively. The results of this procedure in the 10 patients with multiple sclerosis may be summarized as follows: Eosinophile falls varied from 82 to 100%, with a mean decrease of 98% (Fig. 1). The increase in adrenocortical secretion as indicated by the excretion of 17-ketosteroids revealed a mean rise of 4.2 and 7.7 mg. per 24 hours on the first and second days, respectively. Formaldehydogenic-steroid excretion showed a mean rise of 6.0 mg. per 24 hours on the first day and 5.7 mg. per 24 hours on the second day (Fig. 2).

It may be concluded, therefore, that the adrenocortical response to maximal corticotropin stimulation in patients with multiple sclerosis is entirely normal as determined in this small series of representative cases.

Prolonged Corticotropin Stimulation (Capacity of Adrenal Cortex to Sustain Prolonged Stimulation).—The continued administration of corticotropin by eight-

hour intravenous infusions daily for a 10-day period produced a progressive increase in the level of adrenocortical secretory activity as measured by periodic 17-ketosteroid and formaldehydogenic-steroid excretion (Fig. 2). Mean final levels of 26.1 mg. per 24 hours of 17-ketosteroids and 14.8 mg. per 24 hours of formaldehydogenic-steroids were achieved. These values are exemplary of normal adrenocortical activation pursuant to prolonged and intensive corticotropin stimulation.

COMMENT

A group of 10 patients does not constitute an adequate population for the statistical evaluation of the normal dimensions of a complex biological function. The measurement of adrenocortical activity by the procedures employed in this study depends, however, upon the definition of the maximal range of synthetic and secretory function of which the gland is capable. Therefore, the finding in all cases of a normal response, both immediate and sustained, to maximal corticotropin stimula-

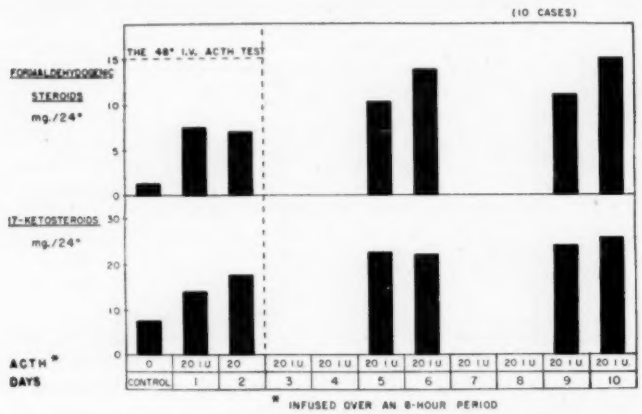

Fig. 2.—Adrenocortical response to daily intravenous infusions of corticotropin to patients with multiple sclerosis.

tion is considered good evidence for the presence of essentially normal secretory mechanisms.

It is of interest to note that the mean control level of 17-ketosteroid excretion in this series is somewhat depressed below normal values. This is a common finding in patients who are chronically ill,[9] the precise mechanism of which is not as yet understood. Since urinary 17-ketosteroids probably represent in part degradation products of oxygenated corticoids, e. g., Compound F (17-hydroxycorticosterone) and cortisone, and in part the products of direct adrenocortical androgen secretion, it is apparent that such a decline in 17-ketosteroid excretion may depend either upon an abnormality in the metabolism of adrenocortical hormones or upon direct suppression of the level of adrenocortical secretion. The latter is a likely possibility

9. Fraser, R. W.; Forbes, A. P.; Albright, F.; Sulkowitch, H., and Reifenstein, E. C., Jr.: Colorimetric Assay of 17-Ketosteroids in Urine: Survey of Use of This Test in Endocrine Investigation, Diagnosis, and Therapy, J. Clin. Endocrinol. **1**:234-256, 1941.

in a neurological disorder such as multiple sclerosis. It now seems well established that the pituitary-adrenal axis is directly influenced by the hypothalamus, probably via a neurohormonal mechanism (Fig. 3). It is important, therefore, to consider the potential effect of central nervous system disease upon the complex function of the hypothalamus, and therefore upon the ultimate disruption of its normal physiological role as the "head ganglion" of the autonomic nervous system and, in all likelihood, of the anterior lobe of the pituitary gland and its target organs. The disruption of the integrated hypothalamus-anterior pituitary unit, with a resultant interference with the normal mechanism of corticotropin release, obviously might result in disordered adrenocortical function, the ultimate result of which is secondary adrenal-cortex inhibition.

Direct quantitative measurement of the actual level of hormones secreted either by the hypothalamus or by the anterior lobe of the pituitary is not now feasible. It

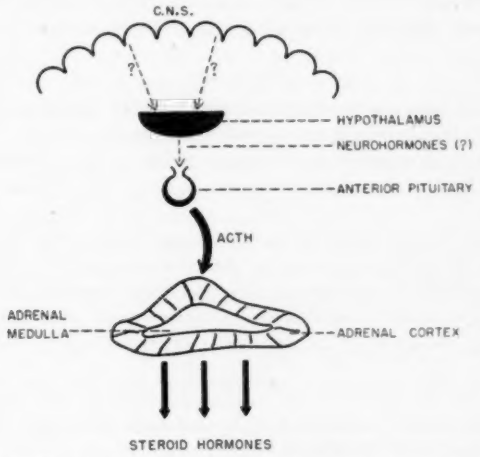

Fig. 3.—The hypothalamus-anterior pituitary-adrenal cortex system.

is necessary, therefore, in order to determine the integrity of the hypothalamus-anterior pituitary-adrenocortical system, to utilize the quantitative methods now available for the evaluation of the functional status of the adrenal cortex. Thus, the pattern of adrenocortical response to the administration of corticotropin may be highly indicative of the functional state of the entire neuroendocrine unit. In the presence of adrenocortical hypofunction secondary to pituitary insufficiency, and presumably of hypothalamic dysfunction, the adrenal response to corticotropin is typically delayed, often as much as three to four days.[10] In the present study the immediate adrenocortical response elicited in both the 4-hour and the 48-hour corticotropin tests would appear to exclude the existence of adrenocortical insufficiency secondary to disturbances in hypothalamus-anterior pituitary function.

10. Venning, E. H., and Browne, J. S. L.: Excretion of Glycogenic Corticoids and of 17-Ketosteroids in Various Endocrine and Other Disorders, J. Clin. Endocrinol. **7**:79-101, 1947.

The demonstration of an immediate and normal response on the part of the adrenal cortex to corticotropin stimulation leaves unanswered, of course, the inherent ability of the gland to maintain a significant secretory response in patients with chronic disease. The 48-hour intravenous test constitutes a maximal stimulus to hormonal synthesis and secretion and is, therefore, a measure of the reserve capacity of the gland to increase significantly its secretory level above that of resting conditions. It is apparent from these studies that adrenocortical reserve in multiple sclerosis is entirely normal.

Considerable emphasis has been laid upon the possible occurrence of "adrenal exhaustion" in conditions of protracted stress. It is therefore pertinent to note that the patients in this study were capable of responding in a normal fashion to the intense stimulation associated with the administration of corticotropin intravenously over a 10-day period. This implies not only the normal capacity to sustain an elevated level of synthesis and secretion but, in all probability, the capacity to undergo further structural hyperplasia. Thus, the adrenocortical function in this group of patients in no way suggests a state of adrenal exhaustion.

SUMMARY

Adrenocortical response to corticotropin (ACTH) appeared to be normal in 10 patients with classic, long-standing multiple sclerosis.

The initial state of adrenocortical function in this group of patients appeared to be below optimal, but consistent with that observed in patients suffering from chronic illness.

There is no evidence in the group of patients studied that the specific pathological processes of multiple sclerosis in the central nervous system interfere specifically with hypothalamus-anterior pituitary-adrenal cortex activation.

If the efficacy of adrenocortical-hormone therapy is to be tested in patients with multiple sclerosis, it should be carried out at pharmacological levels and for prolonged periods.

A. H. Holland Jr., M.D., The Armour Laboratories, Chicago; H. F. Hailman, M.D., The Upjohn Company, Kalamazoo, Mich., and E. C. Vonder Heide, M.D., Parke, Davis & Company, Detroit, provided the corticotropin used in this study.

PARALYSIS WITH SADDLE-BLOCK ANESTHESIA IN OBSTETRICS

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ADRIANI and Roman-Vega,[1] in 1946, suggested the term "saddle block" to describe a technique of spinal anesthesia which provides analgesia limited to the saddle area. In essence, this technique is a conduction block of the lower lumbar and sacral segments of the spinal cord by an anesthetic agent dissolved in glucose to produce a hypertonic solution. However, this procedure requires the introduction of an anesthetic agent into the subarachnoid space, thus exposing the patient to the complications associated with any form of spinal anesthesia. It is the purpose of this paper to bring to the attention of physicians (obstetricians and anesthetists in particular) a delayed complication resulting from this type of anesthesia in normal obstetrical deliveries. This study results from our experience with six proved cases of chronic adhesive arachnoiditis following saddle-block anesthesia given at the St. Louis Maternity Hospital during a three-year period.

In spite of many reports on the danger of intrathecal medication, as emphasized by Wilson and associates,[2] Thorsen,[3] Kennedy and associates,[4] Schildt,[5] Smith,[6] Hebert and associates,[7] Bergner and associates,[8] Hyslop,[9] Nicholson and Eversole,[10]

From the Departments of Neuropsychiatry and Obstetrics and Gynecology, and the Division of Neurosurgery, Washington University School of Medicine.

1. Adriani, J., and Roman-Vega, D. A.: Saddle Block Anesthesia, Am. J. Surg. **71**:12-18 (Jan.) 1946.

2. Wilson, G.; Rupp, C., and Wilson, W. W.: The Dangers of Intrathecal Medication, J. A. M. A. **140**:1016 (July 30) 1949.

3. Thorsen, G.: Neurological Complications After Spinal Anesthesia, Acta chir. scandinav. (Supp. 121) **95**:1-272, 1947.

4. Kennedy, F.; Somberg, H. M., and Goldberg, B. R.: Arachnoiditis and Paralysis Following Spinal Anesthesia, J. A. M. A. **129**:664-667 (Nov. 3) 1945. Kennedy, F.; Effron, A. S., and Perry, G.: The Grave Spinal Cord Paralysis Caused by Spinal Anesthesia, Surg., Gynec. & Obst. **91**:385-398 (Oct.) 1950.

5. Schildt, E.: Low Spinal Cord Injuries Following Spinal Anesthesia, Acta chir. scandinav. **95**:101-131, 1947.

6. Smith, W. A.: Neurological Hazards of Spinal Anesthesia, J. M. A. Georgia **22**:297-303 (Aug.) 1933.

7. Hebert, C. L.; Tetirick, C. E., and Ziemba, J. F.: Complications of Spinal Anesthesia, J. A. M. A. **142**:551-557 (Feb. 25) 1950.

(Footnotes continued on next page)

Brock and associates,[11] Ericsson,[12] and Barker and Ford,[12a] during the past several years, this fact is not generally accepted. The fear of complications from spinal anesthesia is thought by many physicians to stem from false concepts on the part of the laity, without clinical substantiation. Because of this situation, we believe that our series of cases should be described in detail to emphasize further the danger of spinal anesthesia, particularly because of its present wide use in obstetrics.

METHODS AND MATERIAL

From June, 1947, to June, 1950, 1,272 obstetrical patients were given "saddle-block" anesthesia at the St. Louis Maternity Hospital.

Since it was known that this procedure was potentially dangerous, a careful routine was carried out under the close supervision of the resident staff experienced in the technique. Contraindications to its use included (1) severe systemic infections and any disease of the skin at the puncture site, (2) extremes of blood pressure, (3) any disease of the central nervous system or spinal cord, and (4) drug allergies. Mild basal barbiturate sedation was used to prevent stimulant effects of the anesthetic agent. The saddle-block anesthesia was induced during the latter part of labor to provide both analgesia and anesthesia for delivery. The actual technique was as follows: With the patient in a sitting position, her back was scrubbed with sterile soap and water, cleansed with ether, and twice coated with merthiolate solution. The operator wore cap and mask, performed a five-minute surgical scrub, and donned sterile gloves. Puncture was accomplished in the fourth or fifth lumbar interspace, the solution injected over a five-second period between uterine contractions, and the patient allowed to remain in the upright position for 30 seconds. After this, she was placed in the supine position, with head and shoulders elevated on a pillow. The blood pressure was recorded at five-minute intervals until the delivery was completed.

All the equipment used in the procedure was autoclaved in the routine manner. The stored ampules of the anesthetic agent were immersed in a 1:1,000 solution of benzalkonium (zephiran®) chloride, colored to allow recognition of cracked ampules. Piperocaine (metycaine®) hydrochloride, in 1.5% solution, 22.5 mg., was used for the first 254 patients but was discontinued because the anesthetic effect lasted only 30 to 40 minutes. Piperocaine hydrochloride U. S. P., 3%, in dextrose solution was used for the next 67 patients, but it also proved unsatisfactory. The remainder of the series (951 patients) received dibucaine (nupercaine®) hydrochloride, 2.5 mg. in 1 cc. of a 5% dextrose solution. This provided anesthesia of two to three hours' duration. A solution of dibucaine is readily precipitated in an alkaline medium,[13] and for this reason the syringes and needles were rinsed with 0.1 N HCL before being autoclaved.

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8. Bergner, R. P.; Roseman, E.; Johnson, H., and Smith, W. R.: Severe Neurologic Complications Following Spinal Anesthesia: Report of 6 Cases, Anesthesiology **12**:717-727 (Nov.) 1951.

9. Hyslop, G. H.: Spinal Anesthesia: Nervous System Sequelae, Surg., Gynec. & Obst. **57**:799-802 (Dec.) 1933.

10. Nicholson, M. H., and Eversole, V. H.: Neurologic Complications of Spinal Anesthesia, J. A. M. A. **132**:679-685 (Nov. 23) 1946.

11. Brock, S.; Bell, A., and Davidson, C.: Nervous Complications Following Spinal Anesthesia: Clinical Study of 7 Cases, with Tissue Study in One Instance, J. A. M. A. **106**:441-447 (Feb. 8) 1936.

12. Ericsson, N. O.: On the Frequency of Complications, Especially Those of Long Duration, After Spinal Anesthesia, Acta. chir. scandinav. **95**:167-191, 1947.

12a. Barker, L. F., and Ford, F. R.: Chronic Arachnoiditis Obliterating Spinal Subarachnoid Space, J. A. M. A. **190**:785-786 (Sept. 4) 1937.

13. Davis, L.; Haven, H.; Given, J. H., and Emmet, J.: Effects ot Spinal Anesthesia on the Spinal Cord and Its Membranes: Experimental Study, J. A. M. A. **97**:1781-1785 (Dec. 12) 1931.

In our series the use of dibucaine as the anesthetic agent resulted in pain-free childbirth. The saddle block enabled the obstetrician to perform all types of instrumentation with the patient relaxed. The babies showed no depression and cried spontaneously. The procedure was without mortality. The only complication during the immediate postpartum period was the occurrence of headache in 20% of patients. The headaches varied from a mild throb to an excruciating pain lasting from one to five days. The patients were without symptoms when they left the hospital and, except for minor neurological complaints in two patients, were asymptomatic at the six-week postpartum examination.

FOLLOW-UP OBSERVATIONS

The follow-up study was planned after the recognition of chronic adhesive arachnoiditis in three young women, all of whom had had spinal anesthesia for delivery. Our purpose was to attempt to discover any unrecognized complications of the saddle-block procedure which may have been too minor to cause the patient to seek medical attention. The effectiveness of our follow-up study is shown in the following tabulation.

Total no. of saddle blocks	1,272
Total no. of ward patients	1,003
Total no. of private patients	106
No. of repeated saddle blocks	163
Follow-up of ward patients	358, or 35.6%

Of the 358 women who responded to our request, 2 were found to have beginning paraplegia. Two others presented themselves before being notified of our survey. Except for a small number whom we were unable to contact, we may assume that those who did not return for the requested examination had no complaints.

Between September, 1950, and May, 1951, all the patients in the ward service who had received saddle-block anesthesia were requested to return for examination. The interval between the administration of the anesthetic and the follow-up examination was three months to four years. These patients were requested to return to the clinic for what was presumably a routine examination by the obstetrical outpatient service. No indication of our interest in spinal anesthesia was given them. Neurological histories of the interval between delivery and the follow-up visit were taken. Neurological examination was performed, with emphasis on the lower extremities.

CASE HISTORIES

CASE 1.—H. W., a 17-year-old Negro primagravida, unipara, delivered an apparently normal child on March 28, 1950, under saddle-block anesthesia (2.5 mg. dibucaine, as heavy solution nupercaine® [14]). The delivery was uneventful, as was the anesthesia, except that the patient noted numbness of her body below the rib margin in spite of the so-called saddle technique.

The postpartum period was normal until the fifth week, when she noted slight numbness and weakness in her feet. She mentioned this at her six-week visit, but the symptom was disregarded as transient. Her condition progressed in severity, and on July 3, 1950, she returned complaining of numbness below the waist, inability to walk without support, and difficulty with urination for the previous two or three weeks.

She was admitted to Barnes Hospital with clinical findings typical of transverse myelitis at the level of the seventh thoracic dermatome and profound motor changes below the iliopsoas muscle group. There were pathological toe signs bilaterally and ankle and knee clonus. Routine laboratory studies and x-rays of the spine revealed nothing abnormal. Lumbar puncture was

14. Heavy solution nupercaine® hydrochloride with dextrose contains 2.5 mg. dibucaine hydrochloride and 50 mg. of dextrose per cubic centimeter.

unsuccessful on three attempts. With ethyl iodophenylundecylate (pantopaque®) inserted into the cisterna magna a subarachnoid block was demonstrated at the level of the eighth thoracic segment. Laminectomy was performed between the 6th and the 10th lumbar vertebra. The dura was observed to be thickened and firmly adherent to the pia-arachnoid. On incision of the dura, the entire spinal cord in the exposed area was found to be surrounded by a dense mass of thickened, adherent arachnoid, which could not be dissected free from the pia and cord. Biopsy confirmed the diagnosis of chronic inflammation of the meninges.

There was temporary improvement for several weeks immediately following operation, but her condition regressed to a point where there was no voluntary activity in her lower extremities. At the time of this report she has no bladder control and requires frequent catheterization. At present she is on a program of physical therapy and vocational rehabilitation.

Case 2.—F. L., a 29-year-old white multigravida, tripara, delivered a normal child on Jan. 3, 1949, under saddle-block anesthesia (heavy solution nupercaine,® 3.75 mg. of dibucaine hydrochloride). The delivery was uncomplicated, and the anesthesia was classic in the distribution of hypalgesia. There was complete recovery in two hours. She remained well for nine months, but in September, 1949, she noted numbness of both thighs and legs, the sensory loss being slightly more marked on the right. There was slow progression, and by June, 1950, the numbness had extended to the saddle area. It was associated with slight weakness of both legs and an unsteady gait. She had also noted hesitancy in voiding and, on at least one occasion, incontinence of urine.

She was admitted to Barnes Hospital on July 2, 1950, at which time physical examination revealed an obese white woman, who walked slowly and unsteadily. There were sensory deficit below the third lumbar dermatome, a diminished right knee reflex, absence of ankle jerks, and no plantar response. Both the gluteal and the anterior tibial group of muscles were weak. There was moderate anal relaxation. Routine laboratory studies and roentgenograms of the spine showed nothing abnormal. Lumber puncture below the first lumbar segment was unsuccessful, but at that level the cerebrospinal fluid dynamics and chemistry were normal. A cystometrogram showed a hypotonic bladder with residual urine. Ethyl iodophenylundecylate inserted at the 12th thoracic level showed a complete block at the 1st lumbar segment. Laminectomy was performed between the 12th thoracic and the 3d lumbar vertebra. The dura was found to be thickened and adherent to the pia-arachnoid. It was possible to free some of the adhesions. Biopsy showed chronic inflammation of the meninges.

The patient showed no improvement after operation and has been readmitted twice for acute urinary retention. She is able to move about with crutches but cannot manage her household duties. She is now on a program of physical therapy and vocational rehabilitation.

Case 3.—M. A., a 40-year-old white primagravida, unipara, was delivered of a normal infant on March 1, 1950, under saddle-block anesthesia (heavy solution nupercaine®; dibucaine hydrochloride, 2.5 mg.), which produced satisfactory hypalgesia up to the rib margin. The postpartum period was normal until the third month, when the patient noted the onset of intermittent headache and back pain. After one month these symptoms disappeared but were replaced by progressive numbness, which within two weeks had involved the area previously anesthetized. Associated with the numbness was progressive weakness in both legs to the extent that the patient was unable to walk without assistance. She had no bowel or bladder difficulty. She was admitted to Barnes Hospital on July 3, 1950. Physical examination revealed a thin white woman who walked only with assistance and then showed a slow, spastic gait. Routine laboratory studies and roentgenograms of the spine disclosed a normal condition. There was a severe sensory deficit below the seventh thoracic dermatome. The abdominal skin reflexes were absent; the knee and ankle jerks were hyperactive and equal; patellar and ankle clonus was present, and pathological toe signs were present bilaterally. There was pronounced weakness in all muscle groups of both lower extremities. No fluid was obtained on spinal puncture below the first lumbar vertebra, but at this level a dark-yellow fluid, containing more than 590 mg. of protein, was found. Ethyl iodophenylundecylate inserted at this level showed a block at the seventh

thoracic vertebra. Laminectomy was performed between the sixth and the eighth thoracic vertebra. The dura was found to be thickened and adherent to the pia-arachnoid, which appeared to be strangulating the spinal cord. The dura was allowed to remain open.

There was no improvement after operation. At present she is unable to walk and has considerable urinary difficulty. She is on a program of physical therapy and vocational rehabilitation.

CASE 4.—F. W., an 18-year-old Negro secundagravida, bipara, had saddle-block anesthesia induced with 3% piperocaine hydrochloride in January, 1949, and 2.5 mg. of dibucaine hydrochloride in February, 1950. Both deliveries were uncomplicated, as were the anesthesias. She remained well until January, 1951, when she noted headaches and numbness, progressing gradually upward to the level of the umbilicus. There was some jerking of her legs. She noted weakness of her legs, which was severer on the left. There was backache, and just before admission she noted hesitancy on urination. Physical examination showed a normal status except for the neurological findings. There was weakness of all muscle groups of the lower extremities, more pronounced on the left side. Appreciation of position was diminished in the lower extremities, and hypalgesia extended up to the 10th thoracic dermatome. Deep reflexes were absent in the legs.

The results of routine laboratory studies were normal. Lumbar puncture was unsuccessful on several attempts. On March 12, 1951, cisterna-magna puncture was done and ethyl iodophenylundecylate was injected. There was complete block at the 10th thoracic segment, with an irregular outline of the roentgenologically opaque material.

She refused to undergo operation and was treated with physical therapy. There was little change in the findings.

CASE 5.—J. W., an 18-year-old Negro primagravida, unipara, delivered a normal child on May 10, 1950, under saddle-block anesthesia (heavy solution nupercaine®; dibucaine hydrochloride, 2.5 mg.). Delivery and anesthesia were uncomplicated. In October, 1950, she noted progressive numbness of the thighs and lower abdomen. In January, 1951, she noted progressive weakness of her legs and on two occasions fell to the ground because of unsteadiness. She had also noted some difficulty with urination.

Abnormal physical findings were limited to the nervous system and consisted of hypesthesia and hypalgesia below the seventh thoracic dermatome. There was slight weakness of all muscle groups of both legs. Abdominal skin reflexes were absent. Deep reflexes were equal and active on the two sides.

Roentgenograms of the spine and routine laboratory studies revealed nothing abnormal. Lumbar puncture was unsuccessful on numerous attempts. Although the needle was felt to have entered the subarachnoid space, no fluid could be obtained. Cystometrograms revealed a neurogenic bladder. Myelography was attempted through the lumbar route but was unsuccessful, presumably because of dense arachnoiditis involving the cauda equina.

The patient refused to have laminectomy and was placed under cortisone therapy, for a total dose of 1,300 mg. There was some improvement on this regimen, with recession of hypalgesia and hypesthesia to the saddle area and some increase in strength. She continued to receive cortisone therapy intermittently and was placed on a physical-therapy program, but has not continued to show improvement.

CASE 6.—B. M., a 27-year-old primagravida, unipara, was delivered of a normal infant at St. Louis Maternity Hospital on April 28, 1950, under saddle-block anesthesia (1 cc. of 3% piperocaine hydrochloride). The delivery and postpartum course were not remarkable. She was essentially well until June, 1951, when she first noted that her legs felt somewhat heavy and she was beginning to be uncertain of her balance. She also noted that the floor seemed to her to feel hot. These symptoms progressed until her admission to Barnes Hospital, on Dec. 11, 1951.

Physical examination on admission showed that the vital signs were normal. General examination revealed nothing remarkable. Neurological examination revealed an unsteady gait, and she swayed in the Romberg position. The quadriceps were weak bilaterally, especially on the left side. There was also weakness of the muscles in the leg and the foot on the left, with

associated left foot drop. The deep reflexes were slightly hypoactive but equal bilaterally. The abdominal skin reflexes were absent, and there was no response to plantar stimulation. Sensory examination revealed patches of diminished to no sensitivity to pinprick, heat, and touch, extending from the level of the eighth thoracic to the fifth lumbar dermatome bilaterally. There appeared to be diminution of the appreciation of vibration over the iliac crests and the patellae. The appreciation of position was intact in the lower extremities.

Routine laboratory examination revealed nothing remarkable. Lumbar puncture revealed an initial pressure of 135 mm. of spinal fluid. The Cone test gave the findings of almost complete block. The spinal fluid protein was 197 mg. per 100 cc. The colloidal gold curve was normal, and the Wassermann reaction was negative. Myelograms with ethyl iodophenylundecylate revealed a partial block between the first and the second lumbar vertebra, with a rounded filling defect on the left side. Because of the possibility of tumor, the patient underwent an explorative laminectomy. No tumor was present, and the diagnosis of adhesive arachnoiditis was obvious.

The patient improved after operation. She was then given a course of cortisone therapy, a total of 1 gm. being administered over a period of 13 days. On this regimen she noted striking diminution of sensory loss, as well as an increase in muscular strength in the lower extremities. At the time of discharge she was able to walk well.[15]

COMMENT

In these young healthy women neurological complications might possibly be due to some error in technique, to faulty solutions used in intrathecal injection, or to a contaminant introduced during the administration of the anesthetic. The administration of the anesthetic was carefully supervised by well-trained men, experienced in the technique. Ampules containing glass fragments subsequent to their opening were discarded. Coloring material was added to the sterilizing solution to prevent the use of cracked ampules which had possibly leaked or which had become contaminated. We believe that this part of the technique is blameless.

The care of equipment used in this type of procedure is important, and we have scrutinized this closely. The syringes and needles were washed with green soap and rinsed several times with water. They were then rinsed with 0.1 N HCL. We were somewhat concerned about the latter, but actual titration experiments failed to demonstrate any residual acidity following autoclaving. Winkelman [16] described 11 patients showing varying degrees of neurological damage following the accidental introduction of "algono," a detergent used for washing syringes, with the anesthetic agent. In his cases the syringes were washed with the detergent and rinsed once or twice with tap water before being autoclaved. His patients differed from ours in several ways: The onset of symptoms occurred only a few days after injection, instead of several months. About one-half his patients had cerebral arachnoiditis with partial spinal block. Six of his 11 patients recovered almost completely, while ours have progressed to paralysis of long duration.

The possibility that a faulty lot of anesthetic agent was responsible is discounted by the fact that the cases in which arachnoiditis developed were widely scattered in

15. We know of a seventh case in which the clinical picture was similar to that in the cases already described, in which paraplegia developed three to four months after saddle-block anesthesia for delivery. However, we have not included the patient in this series for the reason that we are unable to substantiate the diagnosis of chronic adhesive arachnoiditis from the findings made available to us. In any event, we strongly suspect that this patient represents another case of a serious complication from spinal anesthesia used for obstetrical delivery.

16. Winkelman, N. W.: Neurologic Symptoms Following Accidental Intraspinal Detergent Injection, Neurology **2**:284-291 (July-Aug.) 1952.

time (1947 to 1950). Furthermore, in other cases in which anesthesia was induced with the same lot of drug neurological complications did not occur.

Evidence has been presented by some authors [17] to show that neurotoxicity exists in all anesthetic agents, and is manifested most strikingly at the site of injection, owing probably to greater concentration at that point. This toxicity is manifested by (*a*) varying degrees of meningeal irritation, (*b*) swelling of ganglion cells with disappearance of cell fibrils, (*c*) swelling and degeneration of the axis-cylinders of the nerve roots, and (*d*) peripheral degeneration of the myelin sheath of the spinal cord. In our series complications have followed use both of dibucaine and piperocaine (one case only).

That this is not a rare syndrome is attested by the many reports describing similar cases. Kennedy [4] described 3 such cases in 1945 and 12 more in 1950. Thorsen [3] described a number of such complications in 1947, and recently six cases were reported from Louisville.[5]

There have been several reports of complications of spinal anesthesia in obstetrical patients. Three of Kennedy's patients underwent Caesarean section, and arachnoiditis later developed. Walker and Matthews [18] described two cases of sudden death accompanying spinal anesthesia preparatory to delivery. It has been suggested by Federighi [19] that there is increased sensitivity to spinal anesthesia in gravid women. Why this should be true is not clearly understood. It is assumed that the circulation through the vertebral vascular system may be impaired by the increased abdominal pressure during labor, and thus a higher concentration of the drug may persist in the spinal subarachnoid space for a longer time. The fact that more cases have not been reported may be due to the long interval between the saddle-block anesthesia and the onset of neurological symptoms. Although two of our patients complained of mild symptoms six weeks after delivery, examination did not reveal impairment of function at that time. It is our opinion that the causal relationship of spinal anesthesia to arachnoiditis in many of these cases may be overlooked because of the latent period, the patient having been discharged by the obstetrician long before symptoms appear. There are many reports of large series of spinal anesthesia without complication, but in most instances the patient is lost sight of with discharge from the hospital, some 10 days to 2 weeks after delivery or operation, as the case may be.[20]

Many authors have reported on the efficacy of low-spinal anesthesia in routine obstetrical practice,[21] with little evidence of serious complications. Greenhill [22] has posed a question, "Shall spinal anesthesia be used in obstetrics?" Our answer, based

17. Davis and others.[13] Lundy, J. S.; Essex, H. E., and Kernohan, J. W.: Experiments with Anesthetics, J. A. M. A. **101**:1546-1550 (Nov. 11) 1933.

18. Walker, H. C., and Matthews, H.: Two Successful Post-Mortem Caesarian Sections Following Spinal Anesthesia, Brit. M. J. **1**:938 (April 22) 1950.

19. Federighi, G.: Giorn. ital. anest. **5**:292, 1939.

20. Hebert and others.[7] Lahey, F. H.: Symposium on Spinal Anesthesia: Introduction, S. Clin. North America **20**:767-780 (June) 1940.

21. Buerger, C. L., Jr.: Saddle Block Anesthesia in Obstetrics, J. M. A. Alabama **19**:157-160 (Dec.) 1949.

22. Greenhill, J. P.: Shall Spinal Anesthesia Be Used in Obstetrics? Anesthesiology **11**:283-288 (May) 1950.

on the findings in this series and the fact that childbirth is a perfectly normal function, is that it would seem unwise to subject the healthy young mother to a procedure which carries even the smallest risk of permanent paralysis. In our series the incidence was 0.47%, and because of this risk the use of low-spinal anesthesia for routine deliveries at St. Louis Maternity Hospital has been discontinued.

SUMMARY AND CONCLUSIONS

Six cases of chronic adhesive arachnoiditis with severe residual paralysis following spinal anesthesia for obstetrical delivery in 1,272 patients are presented. This incidence is 0.47%.

The fact that more cases of this type have not been reported may be due to the long latency (weeks to months) between the spinal anesthesia and the onset of symptoms.

Spinal anesthesia is too dangerous to justify its use in the uncomplicated obstetrical case.

ALLERGIC ENCEPHALOPATHY WITH PAPILLEDEMA

Report of a Case

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THERE are few reports in the literature concerning allergic involvement of the central nervous system in man. Only five cases of papilledema thought to be due to allergic response [1] have been reported. There are occasional reports of central-nervous-system reactions to rabies immunization that are probably on an allergic basis.[2] Experimental work has suggested that certain of the demyelinating diseases may be allergic in nature.[3] A case of central-nervous-system disorder thought to be of allergic origin is reported. This observation suggests that allergy must be considered in the differential diagnosis of that vague group of disturbances classified as pseudotumor or encephalopathy of undetermined cause.

REPORT OF CASE

F. L., a 9-year-old white boy, was admitted to the Children's Hospital on Jan. 22, 1949, with the following pertinent history: He had had bouts of hay fever and sensitivity to certain foods. About 3½ years before admission he had an episode of headache, lethargy, blurred and double vision, and papilledema, which cleared spontaneously over a short period. The onset of this attack followed a visit to the zoo.

The child had had repeated infections of the upper respiratory tract and on various occasions showed roentgenographic evidence of clouding of the right antrum and the left sphenoid sinus. A year and a half before admission he had had an attack of bilateral otitis media that was followed by pneumococcic meningitis. These conditions were treated successfully with penicillin, and the child recovered without residuals.

Beginning in November, 1948, the child suffered attacks of middle-ear infection on alternate sides. These were treated with heavy doses of penicillin. Late in December he recovered from the otitis media, began to complain of headache, and was admitted to the Miami Valley

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1. Hayden, H. C., and Cushman, B.: Problems in Nutrition in Allergy: Report of a Case of Optic Neuritis on an Allergic Basis, Illinois M. J. **80**:500-503, 1941. Rathgeber, V. D.: Allergic Retrobulbar Neuritis, Texas J. Med. **43**:334-336, 1947. Kennedy, F.: Allergic Manifestations in the Nervous System, New York J. Med. **36**:469-474, 1936.

2. Redewill, F. H., Jr., and Woodward, L. J.: Neurological Complications to Treatment with Rabies Vaccine, California Med. **66**:360-363, 1947.

3. Morgan, I. M.: Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Nervous Tissue, J. Exper. Med. **85**:131-140, 1947. Wolf, A.; Kabat, E. A., and Bezer, A. E.: Pathology of Acute Disseminated Encephalomyelitis Produced Experimentally in the Rhesus Monkey and Its Resemblance to Human Demyelinating Disease, J. Neuropath. & Exper. Neurol. **6**:333-357, 1947.

Hospital, Dayton, Ohio, where papilledema was found. Lumbar puncture revealed a pressure of 230 mm. of water; no cells or bacteria were seen on microscopic examination. The protein was 43 mg. and sugar 78 mg. per 100 cc. He was then transferred to the Children's Hospital, Cincinnati, with the tentative diagnosis of brain abscess.

The father, aged 38, and the mother, aged 36, both had mild allergies, principally of the skin. Both were college graduates. Their economic status was above average. The family life was happy, though the mother was justifiably worried about her son. There was one other sibling, a girl four years younger than the patient, who had never been seriously ill and had no known allergic tendencies.

The child himself was said to have been happy, better than average in school, and well adjusted with his playmates. His height was average; he was slightly underweight, and not a robust eater. (Since the allergies have been controlled, he eats much better and is over average weight for his height and age.)

On admission he showed evidence of upper respiratory infection, and x-ray examination revealed clouding of the left antrum and ethmoid cells. Both sphenoid sinuses were clear. There was no evidence of middle-ear infection at that time. The rest of the physical examination showed nothing abnormal. The neurological status was normal except for moderate papilledema (2 to 3 D), present bilaterally but slightly greater on the left. The retinal veins were dilated and engorged. The visual acuity and visual fields were normal on gross testing. Results of laboratory studies were normal; specifically, on admission the hemoglobin was 15.8 gm. per 100 cc.; the red blood cell count 5,630,000, and the white cell count 6,150, with 35% neutrophiles, 2% eosinophiles, 1% basophiles, 48% lymphocytes, and 14% monocytes. Repeated counts were in the same range.

Owing to the atypical history and absence of localizing signs that might be expected with an abscess of otitic origin, the child was observed closely for six days. Little change was noted save a slight increase in papilledema.

On Jan. 28, with the patient under general anesthesia, a lumbar puncture was cautiously performed in the operating room. The fluid overflowed the top of a 600-mm. manometer. The needle was withdrawn immediately. The ventriculographic procedure was then carried out through occipital burr holes. Roentgenograms revealed a small, symmetrical ventricular system. The fourth ventricle was well filled, as were the basilar cisterns; and there was air over the convexities. A space-consuming intracranial lesion having been ruled out, it was thought that the pathological process represented diffuse encephalopathy, probably an unusual allergic manifestation.

On Jan. 31, 1949, the child was given skin tests, with the following reactions: egg, 4+; dust and chicken, 3+; cat dander, chocolate, lamb, and milk, 2+. Tests with several fungi also gave positive reactions. These tests were associated with marked increase in headache and lethargy. Therefore further testing was stopped, and on Feb. 5 the child was given diphenhydramine hydrochloride (elixir of benadryl®) in doses of 3 teaspoons every eight hours. A remarkable alleviation of headache occurred within the first 12 hours. On Feb. 7 there was thought to be diminution in the papilledema. On that day lumbar puncture revealed a pressure of 120 mm. of water, in contrast to the readings on several previous taps done after the ventriculogram, all of them having shown initial pressures in the range of 500 to 600 mm. As these taps were primarily therapeutic, for relief of pressure, laboratory analysis of the fluid was not made.

Only once during this period, on Jan. 27, did the child complain of transient blurring of vision. He was discharged from the hospital on Feb. 17, 1949, symptomatically well but with minimal residual swelling of the disks.

The diphenhydramine medication was continued. On the basis of the incomplete skin tests, it was suggested that eggs be eliminated from the diet, that chocolate, lamb, and chicken be restricted, and that milk be limited to 1 pt. (500 cc.) a day.

The child has been followed by one of us (J. H. S.) during the subsequent three years with adequate allergic control, including desensitizing injections of spring-grass, ragweed-pollen, mold, and bacterial vaccines. During this time not only has the child been free of central-nervous-system symptoms, but his chronic and severe upper respiratory infections have been reduced to the average of one mild attack of nasopharyngitis each winter, which has not necessitated antibiotic therapy.

COMMENT

It is difficult to say with assurance whether the changes in the optic disks were caused by local allergic response in the optic nerves, as has been proposed by others,[1a,b] or were a manifestation of the generalized increased pressure.[4] In the few cases reported as instances of allergic retrobulbar neuritis no vascular changes in the retina were described. In our case venous distention and engorgement were quite evident; these signs, with the increased cerebrospinal fluid pressure, favor a generalized increase in intracranial pressure as the mechanism responsible for the papilledema.

It would seem that a diagnosis of allergic encephalopathy can be entertained after a careful history and prompt response to antihistaminic therapy. Proceeding in this manner is possible if the condition has not progressed to the point where air studies are imperative for diagnosis because the patient's life or vision is endangered by increased pressure.

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4. Lauber, H.: Formation of Papilledema, Arch. Ophth. **13**:733-743, 1935.

THE MYOTONIAS

An Electromyographic Study, with Special Reference to Myotonia Acquisita

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ELECTROMYOGRAPHIC [1] investigations of the myotonias reveal a dramatic and pathognomonic picture. Thus, in patients with myotonia congenita (Thomsen's disease), dystrophia myotonica (myotonia atrophica), and myotonia acquisita (Talma's disease)[2] we have found identical abnormal action potentials generated in the skeletal musculature.

These abnormal action potentials are elicited from a myotonic muscle immediately when the needle electrode is inserted into such a muscle. Large bursts of spontaneous, involuntary motor-unit voltages are seen in the cathode-ray oscilloscope, accompanied by a high-pitched, pulsating sound. Both the abnormal wave forms and the sounds reach a peak immediately and then gradually recede to an isoelectric level and silence. The slightest motion of the needle electrode in the hyperirritable muscle reproduces this characteristic response, which is seen and heard only in a myotonic muscle. Voluntary motion of the muscle produces normal, simple motor-unit contraction voltages, which persist, however, for a considerable period after motor relaxation is attempted by the patient. When the myotonic muscle is at rest, we have never found denervation fibrillation potentials, even though the muscle tested may be clinically atrophied. It is probably safe to say, therefore, that lower motor-neuron disease does not occur in pure myotonia.

REPORT OF CASES

The following case illustrates how the electromyogram can be of value in the early diagnosis of myotonia appearing after trauma (myotonia acquisita).

B. G., a 36-year-old white man, a laborer, entered with the chief complaint of pain low in the back, accompanied by weakness and stiffness of both lower extremities. He stated that two months previously, while working in a slaughterhouse, he slipped from a bloody platform, falling 5 ft. (1.5 meters), to strike the low back, right shoulder, and head on a concrete projection. He stated that for about 10 minutes he was paralyzed from the waist down except that he could move his toes. Gradually the numbness and paralysis of his legs disappeared and were replaced by severe pain in his low back, buttocks, and legs.

Presented before the Western Society of Electro-Encephalography at Pebble Beach, Calif., March 2, 1952.

1. The instrument used was the Meditron Clinical Electromyograph, Model 201.

2. Talma, S.: Deutsche Ztschr. Nervenh. **2**:210, 1892.

He was hospitalized for five days. X-ray examinations revealed no evidence of fracture or dislocation. He had a severe ecchymosis from the level of the iliac crests to the midportion of the thighs. There were no abnormalities of bowel or bladder function. On becoming ambulatory, he continued to suffer from severe low-back and leg pains. His gait was stiff, especially upon his arising from a sitting position, but he "limbered up" after a few steps.

Neurological examination two months after his injury revealed no abnormality of the cranial nerves or the motor, sensory, or reflex systems. There was tenderness on palpation of the lumbosacral region, with spasm of the erector spinae group bilaterally. Forward flexion was limited to about 25% of normal.

Because of the history of temporary paralysis of the lower extremities, the patient was referred for a routine electromyographic study. Unexpectedly, this examination revealed the unmistakable evidence of myotonia, largely confined to the muscles of the lower extremities, buttocks, and low back, but present to a less degree in the muscles of the upper extremities. A repeated neurological examination failed to reveal any true clinical evidence of myotonia.

A careful genealogical survey brought forth no evidence of a familial history of any neurological disorder even remotely suggestive of myotonia.

Within six months the patient had progressed to the point where he had a full-blown clinical myotonic syndrome without focal atrophy or hypertrophy of the affected muscles. He lost 25 lb. (11.3 kg.) in weight and had difficulty in turning his head and initiating locomotion. Since that time, a period of 18 months, his condition has remained approximately the same, without the appearance of baldness, cataract, testicular atrophy, impotence, or any endocrine disturbance.

This case presents evidence of a widespread myotonia, apparently involving all the skeletal musculature, which appeared after trauma. There was no familial or congenital history.

In addition to this case, we have noticed, on occasion, the appearance in the electromyogram, of characteristic myotonic action potentials in isolated traumatized muscles. These action potentials are spontaneous and involuntary, appearing on irritation of the muscle with movement of the implanted needle electrode, just as occurs in the classic forms of myotonia. We have found, however, that the wave forms elicited from the isolated traumatized muscle are of a shorter duration and are much less frequently encountered than in the muscle of a patient with the classic myotonic syndrome. Clinically, of course, there is no obvious manifestation of abnormal excitability of the traumatized muscle. There is, however, the common complaint of stiffness and increased tension in the affected muscle. Could these symptoms, in certain cases, be due to a subclinical, localized, myotonia actually brought on by trauma?

COMMENT

A review of the rather limited literature on myotonia acquisita reveals that true myotonia has appeared after such varied afflictions as focal infection, alcoholism, tuberculosis, typhoid, lead poisoning, gastroenteritis, and cholelithiasis. Only five cases have been reported in which the condition followed direct trauma. Jacoby [3] reported the case of a pianist in whom a hypertrophic form of myotonia of the neck, shoulders, and arms developed shortly after a fall on the palms of both hands. Lhermitte [4] described hypertrophic myotonia of the muscles served by a sciatic nerve

3. Jacoby, G. W.: On Myotonia, J. Nerv. & Ment. Dis. **25**:508, 1898.

4. Lhermitte, J.: Hypertrophie des muscles de la jambe consécutive a une lésion du nerf sciatique par balle, Rev. neurol. **33**:56, 1918.

which had been injured by a bullet. Rimbaud and Jourdan [5] reported generalized myotonia following direct trauma to the limbs. In the case of Huet and Français, cited by Krabbe,[6] myotonia developed one month after prostration following a torpedo explosion. Moore [7] described a patient with myotonia and muscular hypertrophy of both legs following a crushing injury. Our patient had rapid development of a subclinical myotonia, which was diagnosed by the electromyogram a considerable time before the disease became clinically apparent. So far in this case there has been no appearance of hypertrophy of the musculature, such as has been described in several of the other cases after trauma.

It becomes apparent from these six cases of myotonia acquisita following trauma that there are certain significant differences between this form and the classic forms. The acquired type differs from myotonia congenita (Thomsen's disease) in that there is no heredofamilial history and no generalized muscular hypertrophy, and that the onset of the disease occurs in adult life. It differs from dystrophia myotonica (myotonia atrophica) in that, again, there is no heredofamilial factor and the dystrophic features, such as generalized wasting, cataract, baldness, testicular atrophy, impotence, and various endocrine disturbances, do not occur.

Since we have found, occasionally, electromyographic evidence of subclinical focal myotonia in portions of traumatized muscles in certain persons, we ask whether it is possible that in these patients there is an underlying predisposition to myotonia. If this exists, it is interesting to speculate whether or not the reported cases of myotonia acquisita are merely those in which this tendency has become clinically apparent. The mechanism whereby trauma could initiate this subclinical or clinical appearance of myotonia remains to be explained. Krabbe [6] postulated that in all cases of myotonia acquisita there was some degree of polyneuritis. In our case of widespread myotonia following trauma, however, we can find no clinical or electromyographic evidence of such a lower motor-neuron disease, just as is the case in the heredofamilial forms.

CONCLUSIONS

The myotonias may be diagnosed with certainty by a characteristic electromyographic picture. No evidence of lower motor-neuron disease is found.

A case of myotonia acquisita (Talma's disease) following trauma is reported.

The electromyographic findings in this case and in certain cases of subclinical acquired myotonia are discussed.

A suggestion is made that persons in whom myotonia acquisita develops have an underlying predisposition to this disease.

5. Rimbaud, and Jourdan, L.: Un cas de maladie de Thomsen, Rev. neurol. **38**:216, 1922.

6. Krabbe, K. H.: The Myotonia Acquisita in Relation to the Post-Neuritic Muscular Hypertrophies, Brain **57**:184, 1934.

7. Moore, M. T.: Myotonia Acquisita, Am. J. Syph. & Neurol. **19**:409, 1935.

SUPRATENTORIAL TUMORS AMONG CHILDREN

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TUMORS above the tentorium cerebelli occur among children less frequently than do infratentorial tumors,[1] the usual ratio of supratentorial to infratentorial tumors being 1 : 2.

The cases which we wish to report were taken from the records at the Mayo Clinic. Of 4,318 verified brain tumors, 518 occurred among children from birth through 14 years of age. The cases were reviewed as to type and location of tumor; age, sex, and survival of patients, and symptoms, signs, and roentgenologic findings related to the tumors. The pertinent literature also was reviewed.

A total of 190 supratentorial tumors were found, 97, or 51.1% of which were recorded as gliomas according to the classification used by Svien, Mabon, Kernohan, and Adson.[2] Fifty-eight of these were astrocytomas; 24, ependymomas; 11, oligodendrogliomas, and 4, neuroastrocytomas. Other supratentorial tumors included 35 craniopharyngiomas, 14 tumors of the pineal body, 12 sarcomas, 12 meningiomas, 9 tumors of the pituitary gland, 7 vascular tumors, 3 epidermoid tumors, and 1 tuberculoma. Keith, Craig, and Kernohan,[3] in 1949, reported that 84% of 427 verified intracranial tumors occurring among children were gliomas, and Bailey and associates [1b] reported that 70% of supratentorial tumors in children were gliomas.

The cases of astrocytomas, ependymomas, oligodendrogliomas, and neuroastrocytomas (Fig. 1) will be discussed under the common headings of gliomas.

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From the Section of Neurologic Surgery (Dr. Craig) and the Section of Pathologic Anatomy (Dr. Kernohan) Mayo Clinic.

1. (*a*) Adson, A. W.: Brain Tumors in Children, Journal-Lancet **58**:207-216 (May) 1938. (*b*) Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939. (*c*) Cushing, H.: The Intracranial Tumors of Preadolescence: Report of a Clinic for the Combined Meeting of the Pediatric Section of the New York Academy of Medicine, the Philadelphia Pediatric Society, and the New England Pediatric Society, held at the Peter Bent Brigham Hospital, Boston, Oct. 16, 1926, Am. J. Dis. Child. **33**:551-584 (April) 1927.

2. Svien, H. J.; Mabon, R. F.; Kernohan, J. W., and Adson, A. W.: A Simplified Classification of the Gliomas, Based on the Concept of Anaplasia, S. Clin. North America **29**:1169-1187 (Aug.) 1949.

3. Keith, H. M.; Craig, W. McK., and Kernohan, J. W.: Brain Tumors in Children, Pediatrics **3**:839-844 (June) 1949.

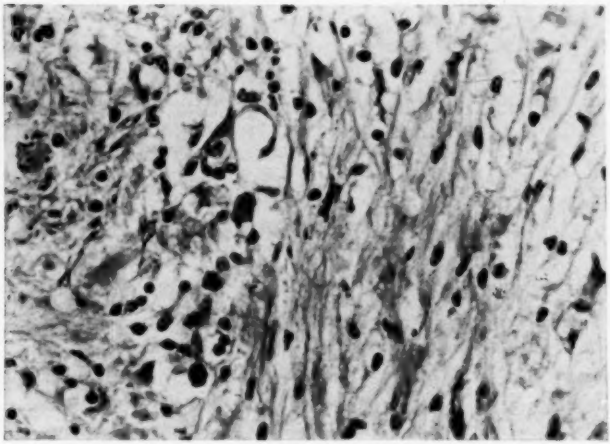

Fig. 1.—Neuroastrocytoma, Grade 3 (hematoxylin and eosin; × 390), in the right temporal lobe of a boy 12 years of age. Note large nerve cell, astrocytes, glial fibrils, and mitotic figures.

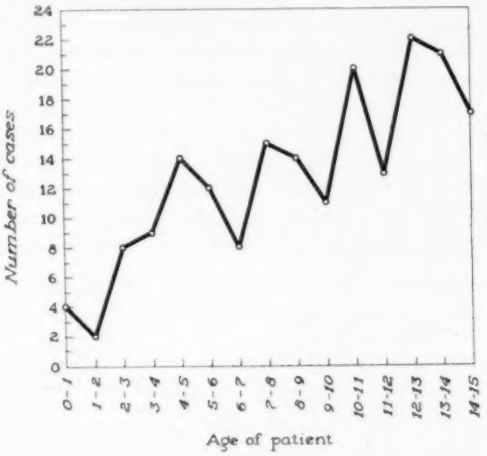

Fig. 2.—Relation of incidence of supratentorial tumors to age of patients.

GLIOMAS

Gliomas were present most commonly among patients from 8 to 14 years of age; the ages of 61 patients were in this range, while the ages of 36 patients ranged from birth through 7 years (Fig. 2). These findings were in agreement with the report of Marburg,[4] in which he stated that gliomas were commoner in the older age group of children. Fifty of the patients were boys and 47 were girls. In accordance with the classification of Svien and associates,[2] the degree of malignancy of 12 tumors was Grade 1; that of 26 tumors, Grade 2; that of 33 tumors, Grade 3, and that of 15 tumors, Grade 4. The remaining 11 tumors, which were oligodendrogliomas, were not graded as to degree of malignancy.

Eighteen gliomas were found in the frontal lobes; 27, in the parietal lobes; 21, in the temporal lobes; 2, in the occipital lobes; 11, in the third ventricle; 4, in the thalamus, and 2, in the midbrain. Eleven astrocytomas of the optic nerve were found, and 1 astrocytoma was reported as being suprasellar. Saebø [5] stated that 88% of tumors of the optic nerve occur before the patient is 20 years of age and that 75% of the gliomas of the optic nerve occur within the first 10 years of life.

Headache (45.4%), vomiting (25.6%), visual disturbances (20.6%), and weakness or paralysis (23.7%) were the commonest presenting complaints among patients with gliomas of the brain. Five patients who complained of proptosis had a glioma of an optic nerve. Bailey and co-workers [1b] stated that visual disturbance among children with brain tumors is an important symptom, as it usually occurs late in the course of the illness. The average duration of symptoms ranged from 6 months to 7½ years. Svien and associates [2] reported the average duration of symptoms among patients of all ages with astrocytomas of Grade 1 as 20.8 months, of Grade 2 as 11.2 months, of Grade 3 as 11.8 months, and of Grade 4 as 7.3 months.

A review of the symptoms and signs in the 97 patients with supratentorial gliomas revealed that 81 had headaches at one time or another during their illness; 66 of these had other evidences of increased intracranial pressure. Seventy-nine patients had a history of vomiting; 62 complained of visual disturbances, 42 of whom had increased intracranial pressure. Thirty-five patients had a history of convulsions, 11 of whom had unilateral convulsions. Bucy and Haverfield [6] reported convulsions as an early symptom among children with tumor of the cerebral hemispheres. Ataxia (43 patients), weakness (39 patients), and paresthesias (43 patients) were other prominent complaints.

Papilledema was found among 85 patients with supratentorial tumors; 42 had paralyses of one or more of the third, fourth, sixth, seventh, or twelfth nerves. The third, sixth, and seventh nerves were most commonly involved. Thirty-three patients exhibited defects of the visual fields, ranging from large scotomas to blindness.

4. Marburg, O.: Some Remarks on Tumors of the Brain in Childhood, J. Nerv. & Ment. Dis. **95**:446-459 (April) 1942.

5. Saebø, J.: Primary Tumour of the Optic Nerve (Glioblastoma Multiforme), Brit. J. Ophth. **33**:701-708 (Nov.) 1949.

6. Bucy, P. C., and Haverfield, W. T.: Tumors of the Brain in Children, J. Florida M. A. **27**:287-293 (Dec.) 1940.

Nystagmus, supposedly uncommon in association with supratentorial lesions, was present in 26 of the 97 patients. Macewen's sign, or cracked-pot resonance, was reported among 38 patients; 37 of these had other evidence of intracranial pressure.

X-ray examination of the skull revealed evidence of abnormal changes in 59 patients. In 43 patients erosion of the sella turcica was evident, and in 39 of these other evidence of increased intracranial pressure was present. Thirty-six patients had separation of the suture lines. The roentgenograms of the skulls of 19 patients revealed abnormal deposits of calcium; 9 of these patients had astrocytomas; 4 had ependymomas, and 6 had oligodendrogliomas. Earnest, Kernohan, and Craig [7] reported that 38.8% of patients with oligodendrogliomas have abnormal deposits of calcium within the tumor, evidence of which can be seen in roentgenograms of the skull.

It is interesting that five patients had clinical evidence of diabetes insipidus: Two had an astrocytoma of the optic chiasm; one, a tumor of the temporal lobe, and one, a tumor of the third ventricle.

Fifteen patients (15.5%) exhibited increased intracranial pressure associated with ataxia and nystagmus; air studies showed hydrocephalus with no other localizing signs. These patients first underwent operation for a lesion of the posterior fossa.

Sixty of 90 patients undergoing surgical measures for removal of supratentorial gliomas were dead at the time of the last report. Survival time subsequent to operation varied from the immediate postoperative period to 17 years. The 30 patients who were alive at the time of the last report had survived from 1 month to 17 years after operation.

The reader is referred to the paper by Svien, Mabon, Kernohan, and Adson [2] for description of the various types and grading of gliomas.

CRANIOPHARYNGIOMAS

The 35 craniopharyngiomas constituted 18.4% of the series being reported. This tumor is thought to develop from small collections of epithelial cells on the pars anterior or stalk of the pituitary body or from cysts developing at the junction of the pars anterior and the pars posterior, where Rathke's pouch meets the downward protrusion from the third ventricle to form the pituitary body in fetal life.[8] Smith and Fincher [9] reported 5% of their series of brain tumors in children as craniopharyngiomas; Walker and Hopple,[10] 5%, and Cushing, 11.7%.[1c]

Of the 35 patients, 18 were boys and 17 were girls. Thirteen patients were in the age range from birth through 7 years, and 22 were in the age range of 8 through

7. Earnest, F., III; Kernohan, J. W., and Craig, W. McK.: Oligodendrogliomas: A Review of 200 Cases, Arch. Neurol. & Psychiat. **63**:964-976 (June) 1950.

8. (*a*) Davis, L.: The Intracranial Tumors of Childhood, S. Clin. North America **13**:1019-1038 (Oct.) 1933. (*b*) Ingraham, F. D., and Scott, H. W., Jr.: Craniopharyngiomas in Children, J. Pediat. **29**:95-116 (July) 1946.

9. Smith, W. A., and Fincher, E. F.: Intracranial Tumors in Children: Preliminary Study of 100 Cases, South. M. J. **35**:547-554 (June) 1942.

10. Walker, A. E., and Hopple, T. L.: Brain Tumors in Children: I. General Considerations, J. Pediat. **35**:671-687 (Dec.) 1949.

14 years. The chief complaints and the numbers of patients presenting each were as follows: headache, 25; vomiting, 10; visual disturbances, 17; ataxia, 2; polyuria and polydipsia, 2, and fever, 1.

Ingraham and Scott [8b] found headache to be the commonest symptom in their series of cases. Love and Marshall [11] reported that 88% of their patients with craniopharyngioma had headache as the first symptom; vomiting was a symptom of 41%, and loss of vision of 25%, of the 100 they studied. The average duration of symptoms was 12 months, and three patients had symptoms for less than 6 months.

Headache, in 31 patients (88.6%); visual disturbances, in 29 (82.9%); visual-field defects, in 21 (60%); vomiting, in 21 (60%); changes in the optic disk, in 24 (68.6%), with atrophy in 6 (17.1%), and papilledema, in 18 (51.4%) were the commonest symptoms and signs presented by our 35 patients with craniopharyn-

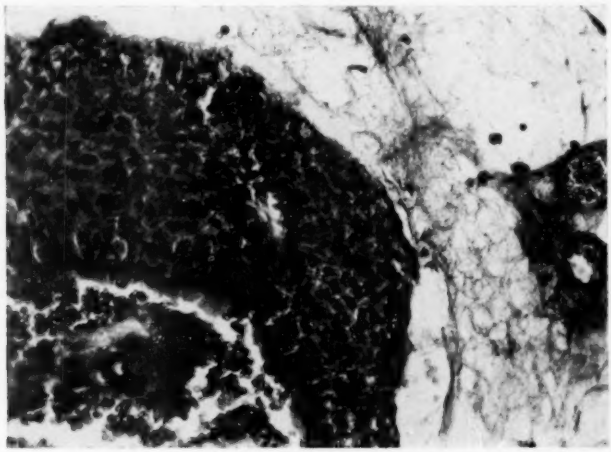

Fig. 3.—Craniopharyngioma (hematoxylin and eosin; × 295) from a boy 10 years of age. Sheets of epithelial cells, loose areolar tissue, deposits of calcium, and a beginning layer of cornification can be seen.

gioma. Seven patients (20%) had evidence of hypothalamic disturbance, and 15 (42.9%) had paralyses of the cranial nerves.

The symptoms and signs most prominent in this series coincide with those reported by Love and Marshall,[11] Ingraham and Scott,[8b] and Adson.[12a] Roentgenograms of the skulls of 31 patients (88.6%) showed evidence of abnormalities. Twenty-eight patients (80%) had abnormal deposits of calcium either above or within the sella turcica; 7 had separation of the cranial sutures, and 29 (82.8%) had changes in the sella turcica. Abnormal deposits of calcium were present in 80% of the cases of craniopharyngioma reported by Cushing,[12] in 85% of those reported

11. Love, J. G., and Marshall, T. M.: Craniopharyngiomas (Pituitary Adamantinomas), Surg., Gynec. & Obst. **90**:591-601 (May) 1950.

12. Cushing, H.: Intracranial Tumors: Notes upon a Series of 2,000 Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

by Carson and Hellwig,[13] in 100% of those reported by Ingraham and Scott,[8b] and in 56% of those reported by Love and Marshall.[11] Four patients in our series had ventriculograms; three showed evidence of changes in the outlines of the third ventricle, and one, evidence of a mass invading the lateral ventricle.

The preoperative diagnosis was correct in 32 (91.4%) of the 35 cases.

In the postoperative period, 20 patients (57.1%) died, and 15 (42.9%) were alive at the time of the last report. Ten patients died in the hospital in the immediate postoperative period, and the other 10 died at intervals of 6 months and 2, 3, 4, and 5 to 10 years after operation. Four patients were alive 4 to 12 months; four patients, 1 to 5 years; six patients, 5 to 10 years, and one patient, 21 years, after operation. Ingraham and Scott [8b] reported a survival rate of 31% for patients with craniopharyngioma; Cushing [1c] reported a survival rate of 14.6% when partial removal was attempted, but 100% of the patients in his series died when complete removal of the tumor was attempted.

Six of the 35 patients in our series received x-ray therapy, and 2 of these 6 were alive 6 months and 21 years, respectively, after treatment. Love and Marshall [11] stated the opinion that 11 of their patients definitely benefited from x-ray treatment.

Craniopharyngiomas might be cystic or solid the sizes ranging from that of a pea to that of a tennis ball. Microscopically, sheets of squamous-epithelium cells were seen, some of which had intercellular bridges but did not contain keratohyalin granules. Cornification was usually present. The epithelium was supported by a characteristic loose areolar tissue (Fig. 3). Calcium was observed in the microscopic sections in 31 cases.

PINEAL TUMORS

Fourteen tumors of the pineal body were found, and these comprised 7.4% of our series of supratentorial tumors. Nine were pinealomas; four, teratomas, and one, an astrocytoma, Grade 4, of the pineal gland. French [14] reported 5 pineal tumors among 146 brain tumors in children; Walker and Hopple,[10] 1; Davis,[8a] 1, and Cushing,[12] 14 pinealomas and 5 teratomas.

Four of the pineal tumors in our series occurred in the years from birth through the 7th year of age, and 10 in the 8th through the 14th year of age. Eight of the patients were boys and six were girls. Haldeman [15] reviewed 113 cases of pineal tumor. All tumors occurred in the second decade (10 to 19 years) of the patient's life; of 102 patients, 78 were males and 24 were females, the sex of the other 11 not being mentioned.

The presenting complaints in our series were as follows: headache, six patients; vomiting, five patients; ataxia, two patients, and drowsiness, nervousness, diabetes insipidus, and precociousness, one patient each. These presenting complaints may be attributed to increased intracranial pressure. Bailey and associates,[1b] Allen and

13. Carson, P. C., and Hellwig, C. A.: Multiple Intracranial Tumors in Children: Suprasellar Adamantinoma Associated with Cerebral Glioma, Am. J. Dis. Child. **46**:119-131 (July) 1933.

14. French, L. A.: Brain Tumors in Children, Minnesota Med. **31**:867-874 (Aug.) 1943.

15. Haldeman, K. O.: Tumors of the Pineal Gland, Arch. Neurol. & Psychiat. **18**:724-754 (Nov.) 1927.

Lovell,[16] and Glaser [17] all found that symptoms of increased pressure were the commonest presenting complaints among patients with pineal tumors. Eleven patients in our series had symptoms less than 12 months before being seen at the clinic, and 3 patients had symptoms for more than one year.

The most prominent symptoms and signs were headache, in 11 patients (78.6%); vomiting, in 11 patients (78.6%); visual disturbance, in 8 patients (57.1%); ataxia, in 7 patients (50%); papilledema, in 13 patients (92.9%), and cranial nerve paralysis, in 9 patients (64.3%). Four patients were found with paralysis of the upward gaze; two, with symptoms referable to the hypothalamus; one, with diabetes insipidus, and one, with precocious sexual development (a boy 8 years of age with a teratoma of the pineal body). Paralysis of the upward gaze and a dilated, fixed pupil may be the only signs, other than increased intracranial pressure, of pineal

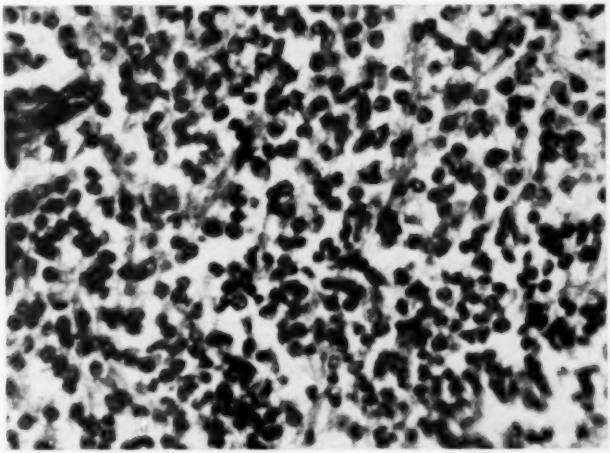

Fig. 4.—Pinealoma (hematoxylin and eosin; × 455) from a boy 3 years of age. The small, dark-staining cells resembled lymphocytes and were surrounded by a layer of lighter-staining nuclei and a moderate amount of fibrous stroma.

tumor. Bailey, Buchanan, and Bucy,[1b] found paralysis of upward gaze in 6 of 11 patients with pineal tumor, and Russell and Sachs [18] found diabetes insipidus in 15 of 58 patients with pinealoma. Bing, Globus, and Simon [19] found sexual precociousness among 10 of 18 patients with teratoma of the pineal body.

16. Allen, S. S., and Lovell, H. W.: Tumors of the Third Ventricle, Arch. Neurol. & Psychiat. **28**:990-1006 (May) 1932.

17. Glaser, M. A.: Tumours of the Pineal, Corpora Quadrigemina and Third Ventricle; the Inter-Relationship of Their Syndromes and Their Surgical Treatment, Brain **52**:226-261 (July) 1929.

18. Russell, W. O., and Sachs, E.: Pinealoma: A Clinicopathologic Study of 7 Cases, with a Review of the Literature, Arch. Path. **35**:869-888 (June) 1943.

19. Bing, J. F.; Globus, J. H., and Simon, H., cited by Russell and Sachs.[18]

In 12 (85.7%) of the 14 patients roentgenograms of the skull showed evidence of the following abnormal changes: abnormal deposits of calcium in the region of the pineal body, 6; separation of the cranial sutures, 7, and erosion of the sella turcica, 8.

Ventriculograms were made on eight patients; all showed evidence of hydrocephalus, and six showed a deformity of the third ventricle.

For one patient only was a preoperative diagnosis of pineal tumor made. For six patients a diagnosis of tumor of the posterior fossa, and for two patients a diagnosis of suprasellar tumor, was made. The latter two patients had diabetes insipidus, and the tumors, which had invaded the third ventricle, had produced a defect in the visual field in one and changes in the sella turcica consistent with a pituitary lesion in the other. All patients having a diagnosis of tumor of the posterior fossa had signs of increased intracranial pressure without localizing signs.

Ten of 13 patients who underwent operation died while still in the hospital, and 1 died two months after surgical intervention. Two patients were alive, at intervals of 2 and 14 years after operation.

Four patients received x-ray therapy after operation; two died, and two were still alive, as just noted.

Grossly, these tumors were circumscribed lesions with a capsule; two had invaded the third ventricle. Microscopically, the pinealomas were composed of large cells, with dark-staining nuclei and granular cytoplasm, arranged in islands which were surrounded by small lymphocyte-like cells in a connective-tissue stroma (Fig. 4). The cells were in varying stages of anaplasia. The teratomas were composed of tissue which was derived from all three embryonal layers of tissue, and they resembled teratomas seen elsewhere in the body. One tumor was an astrocytoma Grade 4, as described in the first group of tumors presented in this paper.

MENINGIOMAS

Meningioma occurs infrequently among children, according to Cushing and Bailey,[20] Stern,[21] Frazier,[22] and Bucy.[23]

Twelve such tumors composed 6.3% of this series, 3 occurring in the age group from birth through 7 years and 9 in the 8- through the 14-year age group. Seven patients were boys and five were girls.

Two tumors were basofrontal, and one was parasagittal in location; two lay over the parietal convexity; two were chiasmal; three were on the frontal convexity, and one each was on the sphenoidal ridge and in the orbit. According to Cushing [12] and Courville,[24] the commonest locations of meningiomas among adults are parasagittal, over the parietal lobe convexity, basofrontal, and on the sphenoidal ridge. French [14] reported 2 cases of meningioma among children, and Smith and Fincher [9] recorded 2 meningiomas among 100 brain tumors in children.

20. Cushing, H., and Bailey, P.: Tumors Arising from the Blood-Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C Thomas, Publisher, 1928.

21. Stern, R. O.: Cerebral Tumours in Children: A Pathological Report, Arch. Dis. Childhood **12**:291-304, 1937.

22. Frazier, C. H.: Brain Tumors in Children, Arch. Pediat. **53**: 295-317 (May) 1936.

23. Bucy, P. C.: Brain Tumors in Children, J. Iowa M. Soc. **29**:47-53 (Feb.) 1939.

24. Courville, C. B.: Pathology of the Central Nervous System: A Study Based upon a Survey of Lesions Found in a Series of 15,000 Autopsies, Mountain View, Calif., Pacific Press Publishing Association, 1937.

Four patients had had symptoms less than one year, four had had symptoms for one to two years, and four had had symptoms from three to eight years, before being seen at the clinic. Bennett [25] reported 39 cases of meningiomas; in 35% symptoms had been present 1 to 5 months; in 42.8%, 6 to 11 months, and in 10%, longer than 2 years.

Patients having meningiomas complained chiefly of headache, visual loss, exophthalmos, vomiting, and convulsions. Exophthalmos and loss of vision were frequently the first symptoms of meningioma of the sphenoidal ridge.[26]

The most prominent symptoms and signs in our series of patients with meningioma were headache, in 8 (66.7%); vomiting, in 5 (41.7%); ataxia, in 6 (50%); visual disturbance, in 10 (83.3%); papilledema, in 6 (50%), and reflex changes, in 6 (50%). Four patients had nystagmus, and three had paralysis of a cranial nerve.

Eight (66.7%) of the 12 patients had changes in the skull, as demonstrated in roentgenograms. Four had abnormal deposits of calcium in the tumor; two had separation of the cranial sutures, and five had evidence of erosion of the sella turcica. Meningioma is more malignant among children than among adults and, in the opinion of French [14] and Buchanan,[27] causes erosion of bone rather than osteomatoid formation.

Ventriculograms were made in two cases; they revealed evidence of a deformity of the third ventricle caused by a basofrontal meningioma in one and evidence of a large tumor of the frontal lobe in the other.

Electroencephalographic studies were carried out in three cases. In one localized delta waves were present over a tumor, and in the other two delta waves were produced over the temporal lobe. A parasagittal lesion was present in one of the latter two cases and a basofrontal lesion in the other.

The tumor was correctly localized in 10 instances (83.3%) before the patients underwent operation. Two patients, one with a tumor of the parietal lobe and the other with a tumor of the frontal lobe, exhibited signs of increased intracranial pressure, without localizing signs; subtemporal decompression was done on one patient and suboccipital decompression on the other.

Sevn patients were dead at the time of the last report. Two died in the immediate postoperative period, and the other five died at intervals of 6 months, 15 months, 2½ years, 5½ years, and 16 years, respectively, after operation.

Of the other five patients two were alive 6 months after operation and one each 22 months, 12 years, and 17 years after operation. Of the two patients who received x-ray therapy subsequent to operation, one died 22 months after treatment and one was alive 6 months after treatment. No patient gave a history of trauma.

These neoplasms were firm, nodular, of moderate size, and composed of tissue derived from the arachnoid membrane. The eight meningothelial meningiomas were

25. Bennett, W. A.: Primary Intracranial Neoplasms in Military Age Group—World War II, Mil. Surgeon **99**:594-652 (Nov.) 1946.

26. Cushing.[12] Horning, E. D., and Kernohan, J. W.: Meningiomas of the Sphenoid Ridge: A Clinicopathologic Study, J. Neuropath. & Exper. Neurol. **9**:373-384 (Oct.) 1950.

27. Buchanan, D.: Primary Intracranial Tumors in Childhood, J. M. A. Alabama **18**:341-348 (June) 1949.

cellular tumors with light-staining, oval or round nuclei with darker-staining reticular formations, tending to form sheets of cells, which in some fields formed whorls (Fig. 5*A*). In some of these whorls psammoma bodies were found. Fibrous

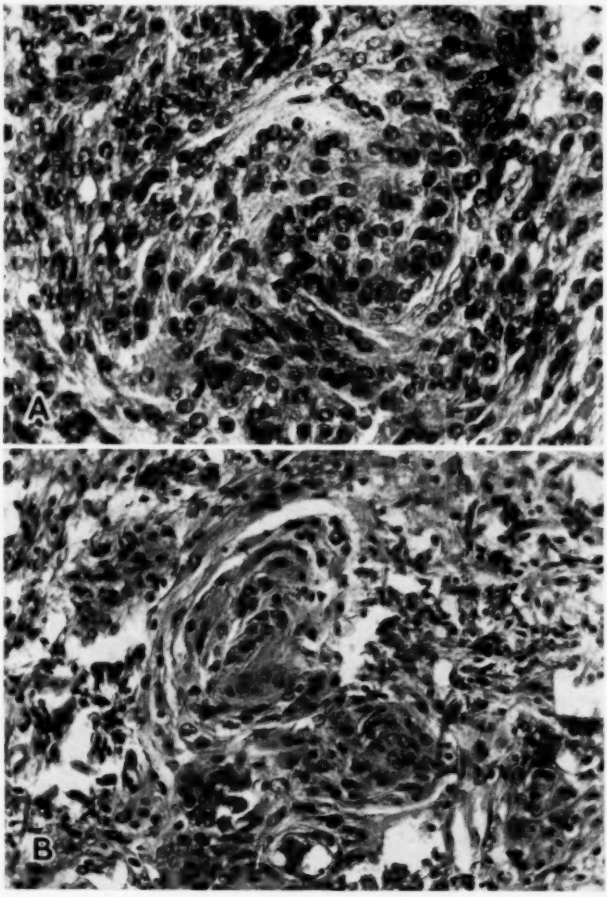

Fig. 5.—*A*, meningothelial meningioma (hematoxylin and eosin; × 320) removed from the left frontal lobe of a 12-year-old girl. Note the whorls of round nuclei with minimal pleomorphism of nuclei and the fibrous appearance of background tissue. Few cells appeared as lipid-containing cells.

B, meningioma of mixed type (hematoxylin and eosin; × 255) from a girl 12 years of age. Whorls of cells and nuclei with fibrous background were seen, and one whorl appeared to be starting a psammomatous area.

meningiomas were not seen in this group, but four tumors were meningiomas of a mixed type. These tumors were composed of a mixture of tissues resembling fibrous meningioma and meningothelial meningioma (Fig. 5 *B*).

SARCOMAS

Twelve (6.3%) of the tumors in this series were sarcomas: Five were fibrosarcomas; 5, perivascular sarcomas, and 2, metastatic tumors, the primary lesion of 1 of these being in the lung and of the other being a lymphosarcoma. Eight of the 12 patients were boys, and 4 were girls; 9 were in the birth through the 7-year age group, and 3 were in the 8- through the 14-year age group. The tumors were found in the frontal, temporal, parietal, and occipital lobes; the septum pellucidum; the orbit, and the base of the skull. Bailey and associates [1b] reported seven sarcomas, all of the cerebellum, in a group of 100 children; Bennett [25] found 5 (1.1%) among young adults. Davis [8a] reported two such tumors among children, and Cushing [12] reported 14 sarcomas among patients of all ages.

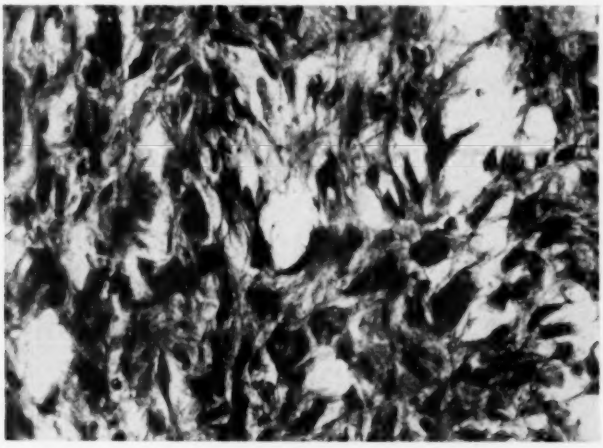

Fig. 6.—Fibrosarcoma, Grade 4 (hematoxylin and eosin; × 320) from the left temporal lobe of a 4-year-old boy. Note the large, light-staining and dark-staining nuclei, mitotic figures, and the fibrous appearance of the cell body.

The chief complaints were as follows: headache, exophthalmos, visual disturbance, and weakness, in two cases each; and convulsions, mass in the abdomen, anemia and jaundice, and an enlarged head, in one case each.

Eight patients had symptoms of less than two months' duration; two had symptoms for less than a year, and two had symptoms for more than a year.

The most prominent symptoms and signs in this group of patients were vomiting, in eight (66.7%); headaches, in five (41.7%); weakness, in four (33.3%); cranial nerve paralyses, in five (41.7%); deep-reflex changes, in five (41.7%), and weakness, nystagmus, and convulsions, in two each (16.7%).

In seven patients (58.3%) abnormalities of the skull were evident roentgenographically. One patient had deposits of calcium in a fibrosarcoma of the dura; one had destruction of the orbit; one had erosion of the sella turcica and five had destruction of the skull due to tumor. In one patient, on whom a ventriculographic study was made, a metastatic tumor was found in the frontal lobe which had produced changes in the outline of the lateral ventricles.

Electroencephalograms in two cases revealed delta activity localized over tumors in the frontal and temporal lobes.

Preoperative location of the tumors was determined correctly for 8 to 10 patients.

Five patients died after operation, three while still in the hospital and two at intervals of 5 and 20 months after operation. At the last report five patients were alive at intervals of one month, two months, five months, one year, and five years. Two of the 12 patients in this series died before surgical procedures could be carried out. Two of the three patients who received x-ray therapy died, and one was still alive two months after treatment. According to the classification by Abbott and Kernohan,[28] the tumors in this group were considered to be fibrosarcomas, perivascular sarcomas, and sarcomas of unknown origin.

The perivascular sarcomas were composed of an extremely cellular tissue with dark, round or oval nuclei and abundant light-staining cytoplasm, and the cells were seen to arise from walls of the blood vessels. Considerable evidence of anaplasia was present, and reticular stains showed fibrils arising from blood vessels. The fibrosarcomas were characterized by spindle-shaped or oval cells with large nuclei in various stages of anaplasia (Fig. 6). The metastatic tumor from the lung was composed of light-staining cells with light nuclei arranged in pseudorosettes around blood vessels.

PITUITARY ADENOMAS

Nine pituitary adenomas were included in this study: Six were chromophobe adenomas; one was an eosinophilic adenoma, and two were malignant adenomas. All patients were more than 8 years of age; five were boys and four were girls. The eosinophilic adenoma occurred in a 13-year-old girl who presented signs of acromegaly. Davis [8a] reported 19 pituitary adenomas among children, and Cushing [1c] reported 2 such tumors among children.

These patients had illnesses ranging in duration from 2 to 54 months, the average being 22.7 months. The initial complaints were as follows: headache and visual disturbance, five patients each; polyuria and polydipsia, two patients, and restlessness, one patient.

Headache occurred among all nine patients, visual disturbances among eight, and vomiting among five. Six patients showed signs and symptoms of hypothalamic disturbance or hypopituitarism; five had bitemporal hemianopsia; three had papilledema; one had atrophy of the optic disk, and two exhibited other cranial nerve paralyses. Grinker and Bucy [29] stated that bitemporal hemianopsia is the commonest field defect seen in association with pituitary tumors. In eight cases roentgenograms showed evidence of changes in the skull; all showed enlargement of the sella turcica. Stenhouse [30] wrote that "enlargement of the sellae without thinning is pathognomonic of pituitary tumors." The one patient without change in the sella turcica had diabetes insipidus of 36 months' duration.

28. Abbott, K. H., and Kernohan, J. W.: Primary Sarcomas of the Brain: Review of the Literature and Report of 12 Cases, Arch. Neurol. & Psychiat. **50**:43-66 (July) 1943.

29. Grinker, R. R., and Bucy, P. C.: Neurology, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1949.

30. Stenhouse, D.: Plain Radiography of the Skull in the Diagnosis of Intracranial Tumours, Brit. J. Radiol. **21**:287-300 (June) 1948.

Preoperative location of the tumor was correct in all cases, and eight patients had parts of their tumors removed by surgical methods; one received x-ray therapy.

Three patients died, two while in the hospital and one three months after operation. Five patients were alive at the time of the last report at postoperative intervals of 1 year, 2 years 10 months, 4 years 9 months, 9 years, and 15 years, respectively. All patients received x-ray therapy after surgical procedures.

The chromophobe adenomas were friable, vascular, encapsulated tumors composed of cellular tissue made up of chromophobe cells (Fig. 7). The cells may be arranged around blood vessels and resemble ependymomas. Some chromophobe adenomas are malignant and seem to occur more commonly among children than adults. The eosinophilic adenoma was a small tumor composed of eosinophilic cells.

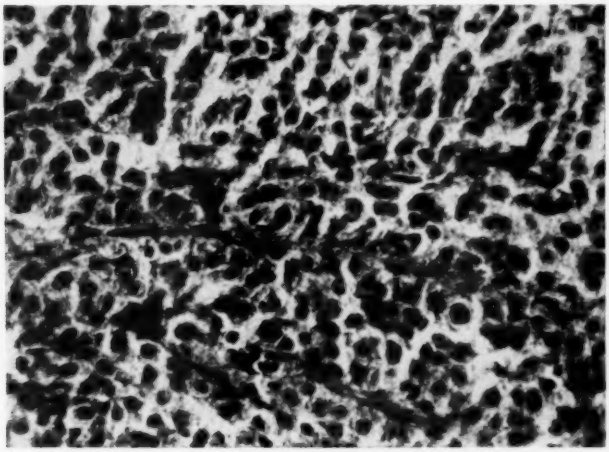

Fig. 7.—A chromophobe adenoma (hematoxylin and eosin; × 320) from a girl 10 years of age showing round cells with large light-staining and dark-staining nuclei arranged along a fibrous stroma.

TUMORS OF BLOOD VESSELS

Seven tumors (3.7%) were classed as tumors of blood vessels. Four of the patients were boys and three were girls. Four patients were less than 7 years of age, and three were in the 8- through the 14-year age group. The tumors were found in the frontal, parietal, temporal, and occipital lobes; the orbit, and the choroid plexus of the third ventricle. In one of the seven cases the diagnosis was Sturge-Weber disease.

French [14] reported 4 supratentorial hemangiomas in 146 brain tumors of children; Davis [8a] reported 5, and Cushing,[12] 2. Boldrey and associates [31] reported 12% of 96 supratentorial tumors of children as tumors of blood vessels.

31. Boldrey, E.; Naffziger, H. C., and Arnstein, L. H.: Signs and Symptoms of Supratentorial Brain Tumors in Childhood, J. Pediat. **37**:463-468 (Oct.) 1950.

The seven patients in our series were ill an average of 27 months before being seen at the clinic; the shortest duration of symptoms was 3 months and the longest 13 years. The initial complaints were enlarged head, 2 patients; tumor of the eye, 2 patients, and nervous spells, convulsions, and loss of vision, 1 patient each.

A history of convulsions was obtained from three patients; headache, from two; vomiting, from two, and visual disturbance, from two. Changes in the skull were evident in the roentgenograms of four patients. Two had abnormal deposits of calcium, one with the characteristic pattern seen in Sturge-Weber disease.[32] Separation of the cranial sutures was noted in roentgenograms of one patient, and enlargement of the orbit was seen in the roentgenogram of another patient.

Electroencephalographic studies were done on three patients. The electroencephalogram for the patient with Sturge-Weber disease showed generalized delta

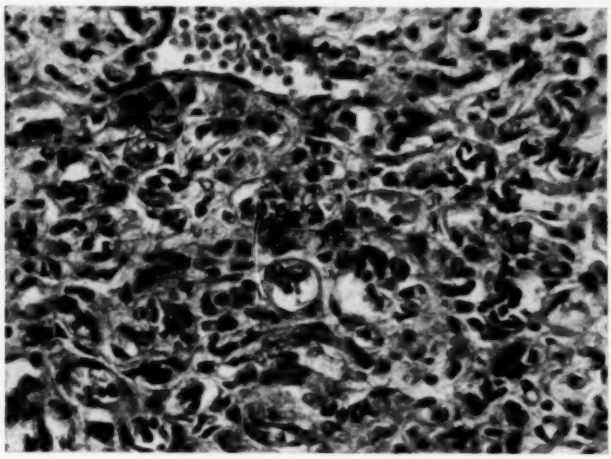

Fig. 8.—Hemangioendothelioma (hematoxylin and eosin; × 415) from the left orbital tumor of an 8-month-old boy showing many cells which were forming vascular spores and an occasional mitotic figure.

activity. The orbital tumor produced occipital delta activity, and one patient had delta activity localized over the tumor in the temporal lobe.

The preoperative location of the tumor was correct in all cases, and in three cases the type of tumor present was diagnosed correctly. All patients underwent operative procedures, and three patients died after operation, two in the immediate postoperative period and one 16 months after operation. Four patients were alive at intervals of 9 months, 7 years, 8½ years, and 12 years 8 months after operation. Four patients received x-ray therapy, three of whom were alive at the time of the last report.

The hemangiomas appeared as collections of well-formed blood vessels. Microscopic examination showed the vessels to be mature, with elastic membranes and

32. Downing, D. F., and Kreidberg, M. B.: Associated Facial and Intracranial Hemangiomas, J. Pediat. **34**:564-573 (May) 1949.

supporting fibrous tissue. Biggart [33] and Kernohan [34] have expressed the opinion that these tumors are congenital maldevelopments of the blood vessels, and not true neoplasms.

The hemangioendotheliomas were of dark, friable tissue, which, on examination, revealed cellular tissue, with light-staining, round nuclei and acidophilic cell bodies which formed numerous blood spaces; small capillaries were seen in the stain for reticulin (Fig. 8). In Sturge-Weber angiomatosis a collection of small blood vessels arises in the pia overlying an atrophied cortex, which contains calcium and iron, usually in the second and third cortical layers. Downing and Kreidberg [32] discussed the cause of this condition.

EPIDERMOIDS

Epidermoids are congenital growths arising from misplaced epithelial tissue, the foundation for which is laid down early in intrauterine life.[35]

Three such tumors were included in this study: one epidermoid of the frontal lobe and two of the skull, the two being included because of their interest to pediatricians, neurosurgeons, and pathologists. All the patients were boys, aged 4, 10, and 13 years, respectively. Walker and Hopple [10] reported the case of a child having an epidermoid cyst of one of the hemispheres.

The two tumors of the skull caused soft, slow-growing masses, present for 3½ and 5 years. The epidermoid of the frontal lobe caused convulsions, which prompted the parents to bring the child for examination. This patient had a history of facial and generalized weakness, nystagmus, and diminished sensation of pain on the side opposite the site of the tumor.

Roentgenograms of the skulls of all the patients exhibited evidence of changes. The two intradiploic tumors produced "punched-out" defects, characteristic of an epidermoid.[36] The tumor of the frontal lobe exhibited deposits of calcium in the surrounding region. Prior to operation, all tumors were diagnosed correctly as to their location, and those of the skull, as to their type. All patients were alive at the last report. Total removal of the tumor must be accomplished, as any small bit of epithelial tissue left behind may allow recurrence of the tumor. The epidermoid is a grossly cystic mass with a tough fibrous capsule. The lining of the cyst is composed of basal and squamous epithelium, the cells containing keratohyalin granules and intracellular bridges. Desquamated cellular debris makes up the contents and causes progressive enlargement of the cyst.

TUBERCULOMAS

One boy, 12 years of age, had a supratentorial tuberculoma in the region of the third ventricle. In 1890, Starr, cited in many papers, reported 300 of 600 tumors of the brain as being tuberculomas. French [14] reported 6 tuberculomas among 146

33. Biggart, J. H.: Pathology of the Nervous System: A Student's Introduction, Ed. 2, Baltimore, Williams & Wilkins Company, 1949.

34. Kernohan, J. W.: Primary Tumors of the Spinal Cord and Intradural Filum Terminale, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, Vol. 3, pp. 991-1025.

35. Love, J. G., and Kernohan, J. W.: Dermoid and Epidermoid Tumors (Cholesteatomas) of Central Nervous System, J. A. M. A. **107**:1876-1883 (Dec. 5) 1936.

36. Adelstein, L. J.: Intradiploic Epidermoid Tumors (Cholesteatoma of the Skull), Am. J. Surg. **78**:480-485 (Oct.) 1949.

tumors in children; Cushing [1c] reported 6 tuberculomas, all in the posterior fossa. Bailey and associates [1b] stated that tuberculomas are four times as common in children as in adults and that they are oftenest found in the posterior fossa. Our patient had a history of headaches and vomiting of 2½ months' duration before being seen. Examination revealed stiff neck; increased reflexes; bilateral paralyses of the third, fourth, and sixth cranial nerves; left homonymous hemianopsia, and papilledema. Studies of the spinal fluid revealed 66 lymphocytes, 13 polymorphonuclear leucocytes, 25 mg. of protein and 48 mg. of sugar, per 100 cc., and a positive culture for tubercle bacilli.

Ventriculograms revealed an incomplete filling of the third ventricle, and surgical measures were carried out after a diagnosis of tumor of the third ventricle or meningitis had been made. The patient died two months after operation.

Grossly, the brain exhibited adhesions over the posterior fossae, purulent material in the ventricle, and a granular, friable mass lateral to the third ventricle.

Chronic inflammation was present, and on microscopic examination many lymphocytes, phagocytes, multinucleated giant cells, fibrin, and calcium were seen. Necrosis and caseation also were present in the tissues, and tubercle bacilli were seen with the aid of special stains. Tuberculosis also was present in one lung of this patient.

COMMENT

The tumors in this group of patients tended to increase in frequency as the ages of the patients increased. This observation is in contrast to the relation of frequency and age given by French [14] and Marburg,[4] who found that the frequency of tumors increased at the ages of 5 to 7 years and of 11 to 14 years. These authors included tumors of the posterior fossa in their discussions, and the occurrence of such tumors in the earlier years of childhood may be the reason for an increase in the 5- to 7-year age group.

As we have mentioned previously, supratentorial tumors occur less frequently than infratentorial tumors among children, the reverse being true among adults.[37] This was evident in our study, as 190 of 518 tumors among children were supratentorial and 328 were infratentorial. Cushing [12] reported a ratio of supratentorial to infratentorial tumors of 4.8:9.5. Bailey, Buchanan, and Bucy [1b] reported 34% of 100 brain tumors of children as supratentorial.

The predominance of gliomas (51.1%) in this study, of which 59.8% were astrocytomas, 24.7% ependymomas, 11.3% oligodendrogliomas, and 4.1% neuroastrocytomas, is comparable to the predominance of gliomatous tumors in other studies, which included patients of all ages. However, the ependymomas and oligodendrogliomas were more prevalent in our study than in other investigations.[38] Cushing [12] reported 2,023 brain tumors, 42.6% of which were gliomas. Of the gliomas, 533 (77.6%) were astrocytomas (classification of Svien, Mabon, and others [2]), 1.3% were ependymomas, and 1.3% were oligodendrogliomas. Courville's [24] study of gliomas revealed 265 astrocytomas, 2 oligodendrogliomas, and 6

37. Adson,[1a] Cushing,[1c] Keith, Craig, and Kernohan.[3]

38. Ringertz, N., and Reymond, A.: Ependymomas and Choroid Plexus Papillomas, J. Neuropath. & Exper. Neurol. **8**:355-380 (Oct.) 1949. Shenkin, H. A.; Grant, F. C., and Drew, J. H.: Postoperative Period of Survival of Patients with Oligodendroglioma of the Brain: Report of 25 Cases, Arch. Psychiat. **58**:710-715 (Dec.) 1947.

ependymomas, among patients of all ages. Bennett,[25] in a report on brain tumors among adults of military age, found that 62% were gliomas; astrocytomas Grades 3 and 4 composed 22.9% of the series, and astrocytomas Grades 1 and 2 composed 14.1% of the gliomas.

The higher grades of astrocytomas are commoner among adults of older age and less common among children, while the lower grades, Grades 1 and 2, are common in the posterior fossa of children.[3]

Ford [39] estimated that 75% of all brain tumors of children are gliomas and that of the remaining 25%, 13% are craniopharyngiomas and 4% are pinealomas.

Craniopharyngiomas are most frequently found among children and young adults. Love and Marshall [11] reported 19 cases of craniopharyngioma in the first decade of life (0 to 9 years), 34 in the second (10 to 19 years), 12 in the third (20 to 29 years), 15 in the fourth (30 to 39 years), 11 in the fifth (40 to 49 years), 8 in the sixth (50 to 59 years) and 1 in the seventh (60 to 69 years). Cushing [12] reported 92 such tumors, the age groups corresponding to those just reported. Among patients less than 20 years of age, presenting endocrine disturbances, headaches, loss of vision, and evidence of suprasellar calcium on x-ray examination, the diagnosis of craniopharyngioma is unequivocal.[11]

Pineal tumors are commonest between the ages of 15 and 30 years in the opinion of Russell and Sachs.[18] Haldeman [15] found the pineal tumors commonest in the second decade of life. Hosoi [40] reviewed the literature and reported that in 52% of the cases studied the patients were less than 20 years of age. Horrax [41] and Haldeman [15] stated that pineal tumors in adults produce signs and symptoms of increased intracranial pressure and pressure on the quadrigeminal plate, while in children they frequently cause disturbances of sexual development. Bailey and co-workers [1b] wrote that disturbances of sexual development are rare in association with pineal tumors, but they do occur; hence a search should be made for a pineal tumor if such disturbances are presented.

Bennett [25] reported 5 sarcomas (1.1%) in his study of young adults, the average age in his group being 28.8 years. The 12 sarcomas in this study constituted 6.3%. Cushing [12] found 11 primary sarcomas (0.7%) in his study.

Of 504 pituitary adenomas recorded at the clinic, 9 occurred among children; Cushing [12] reported 360 (17.8%) in 2,023 intracranial tumors, but only 2 occurred among children. Bailey and associates [1b] and Walker and Hopple [10] did not find any pituitary adenomas in their study of brain tumors in children.

The absence of neurilemmoma is apparent in this study. This tumor is commoner among adults than among children, and 377 (8.7%) of 4,318 brain tumors recorded at the clinic were of this type. Cushing [12] reported 8.7% in his entire series, and Courville,[24] 5.3%.

Vascular tumors also are commoner among adults.[42] No special predilection as to site in the brain was shown by the seven vascular tumors found in our series.

39. Ford, F. R., cited by Bailey, Buchanan, and Bucy.[1b]

40. Hosoi, K.: Teratoma and Teratoid Tumors of Brain, Arch. Path. **9**:1207-1219 (June) 1930.

41. Horrax, G.: Further Observations on Tumor of the Pineal Body, Arch. Neurol. & Psychiat. **35**:215-228 (Feb.) 1936.

42. Naffziger, H. C.: Tumors of the Brain and Spinal Cord, California Med. **70**:424-426 (May) 1949.

Boldrey and associates [31] reported that 12% of supratentorial tumors among children were vascular. Those reported by Cushing [16] were cerebellar in location. Sturge-Weber disease, which causes convulsions and mental deterioration, is recognized oftenest at an early age because a port-wine stain of the face usually accompanies the condition and parents generally seek advice early.[43]

Epidermoids occur most commonly between the anterior perforated space and the foramen magnum.[44] On the basis of location, Love and Kernohan [35] classified the tumors as cerebellar, intraspinal, basofrontal, and intradiploic epidermoids. These tumors grow slowly and produce symptoms by pressure on the adjacent structures; consequently, they are usually seen among adults. Mahoney [45] reported 147 epidermoids, 23 of which were intradiploic, 7 intraspinal, and 117 intracranial; of the last type, 15 were in the fourth ventricle, 44 were parapituitary, and 53 were parapontine. Courville [24] stated that subpial dermoids and epidermoids occur most frequently in the region of the cerebellum and cause symptoms related to the posterior fossa.

SUMMARY

A study was made of the cases of supratentorial tumors among children reported at the Mayo Clinic. Of 190 supratentorial tumors, 97 were gliomas, 58 of these being astrocytomas, 24 ependymomas, 11 oligodendrogliomas, and 4 neuroastrocytomas. Thirty-five craniopharyngiomas and 14 pineal tumors occurred with the next greatest frequency, followed by meningiomas, sarcomas, pituitary adenomas, tumors of blood vessels, epidermoids, and tuberculomas, in the order mentioned.

Sixty-four tumors were present in the region of the third ventricle; the parietal lobe was the next commonest location, followed by the temporal and frontal lobes.

The frequency of occurrence increased as the age of the patients increased. Malignant growths of Grades 2 and 3 occurred most commonly.

Symptoms and signs of increased intracranial pressure, such as headaches, vomiting, visual disturbances, and papilledema, were present most frequently. Changes in the sella turcica, abnormal deposits of calcium, and separation of the cranial sutures were the commonest changes evident on roentgenograms.

Of 34 patients with gliomas, 14 had survived operation for five years or more; and of 16 patients with craniopharyngiomas, 11 had survived for five years.

43. McCoy, A. D., and Voris, H. C.: Sturge-Weber Syndrome, Arch. Neurol. & Psychiat. **59**:504-510 (April) 1948.

44. King, J. E. J.: Extradural Diploic and Intradural Epidermoid Tumors (Cholesteatoma), Ann. Surg. **109**:649-688 (May) 1939.

45. Mahoney, W., cited by King.[44]

STUDIES OF CEREBRAL CIRCULATORY FUNCTIONS FOLLOWING INTRAVENOUS ADMINISTRATION OF PROCAINE HYDROCHLORIDE

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PROCAINE has found its primary usefulness in the past as a local anesthetic agent [1]; indeed, it was thought to be highly dangerous if introduced into the general circulation. Since 1935, when Leriche and Fontaine [2] first deliberately gave the drug intravenously, reports have appeared in the literature with increasing frequency pointing out the beneficial effects of intravascular injection of procaine in a wide variety of conditions. Intravenous administration of procaine has been reported as useful in the treatment of such varied disease states as asthma,[3] arthritis,[4] carbon monoxide poisoning,[5] allergic conditions,[6] cardiac arrhythmias,[7] and a multitude of painful conditions.[8] The physiological mechanisms by which such benefits have been derived have been ill-defined.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, Ed. 1, The Macmillan Company, 1941.

2. Leriche, R., and Fontaine, R.: Les injections intra-artérielles de novocaine dans les affections vasculaires, J. chir. et ann. Soc. belge de chir. **34**:537, 1935.

3. Durieu, H.; de Clercq, F., and Duprez, A.: Traitement de l'asthme par la novocaine intraveineuse, Acta clin. belg. **1**:150, 1946.

4. Graubard, D. J., and Peterson, M. C.: Intravenous Procaine in the Management of Arthritis, Connecticut M. J. **13**:33, 1949.

5. Amyes, E. W.; Ray, J. W., and Brockman, N. W.: Carbon Monoxide Anoxia, J. A. M. A. **142**:1054, 1950.

6. State, D., and Wangensteen, O. H.: Procaine Intravenously in the Treatment of Delayed Serum Sickness, J. A. M. A. **130**:990, 1946.

7. Burstein, C. L.: Utility of Intravenous Procaine in the Anesthetic Management of Cardiac Disturbances, Anesthesiology **10**:133, 1949.

8. (*a*) Gordon, R. A.: Intravenous Procaine for Analgesia in Burns, Canad. M. A. J. **49**:478, 1943. (*b*) Johnson, K., and Gilbert, C. R. A.: Intravenous Procaine for Obstetrical Analgesia, Anesth. & Analg. **25**:133, 1946.

It was thought that study of the effect of intravenous administration of procaine on the cerebral circulatory functions might give valuable information concerning a possible vascular action of the drug. That procaine may possess a vasodilating property when administered intravascularly has been postulated.[9] It has also been noted that "reactions" to procaine are characterized by symptoms of dizziness, confusion, a lowered state of consciousness, and convulsions,[8b] symptoms usually said to be central in origin. The possibility of these symptoms being related to changes in the cerebral circulatory functions caused by procaine seemed worthy of investigation. The purpose of this paper is to report our observations on the effects of intravenous use of procaine on the cerebral circulatory functions in 16 subjects, as measured by the nitrous-oxide technique.[10]

METHOD

Sixteen hospital patients, all men, were chosen. The group included patients with a variety of disease states, as well as normal middle-aged and elderly subjects. A control determination of the cerebral blood flow was performed using the modifications of the original nitrous-oxide technique, previously described.[11] Procaine was then administered intravenously in doses of 0.75 gm. in 250 cc. of isotonic sodium chloride solution over a period of about 15 to 20 minutes. The second blood flow measurement was begun approximately five minutes after the intravenous administration had been started. Arterial pressure measurements were made by the auscultatory method every two minutes throughout the procedures, with the arm held at heart level. Mean pressures were calculated from the formula MP = DP (diastolic pressure) + ⅓ PP (pulse pressure). These readings were checked on several occasions by direct pressure readings on a U-tube mercury manometer, and in all cases calculated and direct pressures agreed closely. Blood samples for oxygen determinations were drawn before and after each blood flow measurement, the average being used as the final arterial-cerebral venous oxygen difference. The oxygen measurements were made by the spectrophotometric method of Hickam and Frayser.[12] Cerebral oxygen consumption and cerebral vascular resistance were calculated in the usual manner. Cerebral venous oxygen tension was not measured directly, but was computed from cerebral venous oxygen content by means of an oxygen dissociation curve drawn for pH 7.4.

RESULTS

The data obtained from these studies are presented in the Table. The only probable significant change in cerebral circulatory function during procaine administration was an increase in cerebral vascular resistance from a mean value of 1.79 to one of 2.08 mm. Hg per milliliter of blood per 100 gm. of brain per minute. Cerebral blood flow, arterial-cerebral venous oxygen difference, mean arterial pressure, and cerebral venous oxygen tension were essentially unchanged.

9. (*a*) Organe, G. S. W., and Scurr, C. F.: Intravenous Procaine in Transfusion, Brit. M. J. **2**:787, 1948. (*b*) Leriche and Fontaine.[2]

10. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of the Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, J. Clin. Invest. **27**:476, 1948.

11. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, with Observations on the Effects of Tilting and Anxiety, J. Clin. Invest. **28**:1163, 1949.

12. Hickam, J. B., and Frayser, R.: Spectrophotometric Determination of Blood Oxygen Content, J. Biol. Chem. **180**:457, 1949.

Cerebral Metabolic Functions Before and After Intravenous Administration of Procaine

Patient No.	Age, Yr.	Diagnosis	Cerebral Blood Flow (Ml./Min./100 Gm. Brain)		Arterial-Cerebral Venous O_2 Difference (Vol. %)		Cerebral O_2 Consumption (Ml. O_2/Min./100 Gm. Brain)		Mean Arterial Pressure (Mm. Hg)		Cerebral Vascular Resistance (Units)		Cerebral Venous O_2 Tension (Mm. Hg)	
			Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	30	Multiple sclerosis	58	50	6.40	7.07	3.71	3.54	91	107	1.57	2.14	33	31
2	58	Rheumatoid arthritis	52	43	7.99	7.22	4.15	3.11	78	80	1.50	1.86	24	23
3	54	Psychosis, undetermined type	39	42	5.59	5.95	2.18	2.50	107	94	2.74	2.24	29	28
4	65	Cerebral arteriosclerosis	46	47	6.36	6.46	2.93	3.03	84	89	1.82	1.89	31	30
5	57	Normal middle age	44	41	6.16	4.36	2.71	1.80	82	99	1.86	2.42	32	38
6	59	Normal middle age	50	57	6.10	6.52	3.05	3.72	99	114	1.98	2.00	31	29
7	59	Cerebral arteriosclerosis	35	36	7.19	8.26	2.52	2.15	105	109	3.00	4.20	30	27
8	32	Multiple sclerosis	56	54	8.01	8.13	4.48	4.39	92	94	1.64	1.74	27	27
9	55	Normal middle age	60	49	7.95	7.62	4.77	3.74	94	84	1.57	1.72	29	29
10	74	Normal old age	49	70	5.01	5.27	2.46	3.69	86	83	1.76	1.19	33	33
11	61	Cirrhosis	49	44	6.03	5.43	2.95	2.39	76	79	1.55	1.80	33	36
12	62	Normal old age	58	67	6.05	6.35	3.51	4.25	100	97	1.73	1.45	34	33
13	58	Peptic ulcer	74	65	6.54	6.11	4.83	3.97	79	85	1.07	1.31	32	34
14	37	Multiple sclerosis	71	48	5.86	6.54	4.16	3.14	89	88	1.25	1.83	35	33
15	65	Normal old age	56	35	7.09	7.10	3.97	2.48	122	119	2.18	3.40	31	28
16	45	Normal middle age	63	46	6.32	7.75	3.98	3.52	92	96	1.46	2.08	31	29
		Mean values	54	49	6.54	6.63	3.52	3.22	92.2	94.8	1.79	2.08	30.9	30.5
		P value	0.12		>0.05		>0.1		>0.2		>0.02		>0.4	

COMMENT

The apparent increase in cerebral vascular resistance following intravenous administration of procaine is indicative of increased tone of cerebral vessels, since there was no significant increase in arterial pressure. In this respect the cerebral vessels apparently differ from those of other parts of the peripheral circulation. Observations by Organe and Scurr indicate that intravenous administration of procaine releases the venous spasm associated with shock.[9a] The observations of Leriche on the intra-arterial and intravenous injection of procaine led him to conclude that the drug had a vasodilating action by virtue of its action on the vascular endothelium.[13] The mechanism for the apparent increase in cerebral vascular tone in our subjects is unexplained by these studies, but, in view of the supposed tendency of procaine to produce vasodilatation elsewhere, it must be a local action of the drug on cerebral vessels. It should be remembered that these studies indicate only the effect of procaine on cerebral vessels in an apparently normal state of tonus and do not give any information concerning the result which might be obtained if the cerebral vessels were already in a state of increased tonus, such as might be expected after cerebral embolism in a young person. Amyes, Ray, and Brockman, in reporting the beneficial effects of intravenous administration of procaine in carbon monoxide poisoning, postulate that the procaine may release the increased cerebral vascular tone thought to occur in this condition.[5]

Although several of our subjects had paresthesias and one suffered slight confusion after the intravenous administration of procaine, there was no change in cerebral circulatory function that might account for such an effect. There was no correlation between the appearance of symptoms and the alteration in the cerebral vascular resistance. It is possible that the procaine has a specific metabolic effect, not measurable by this technique, which was responsible for production of cerebral symptoms.

SUMMARY

Intravenous administration of procaine hydrochloride, in doses of 0.75 gm. administered in 20 minutes, resulted in no significant change in cerebral metabolic functions other than a probable increase in cerebrovascular resistance.

13. Leriche, R.: De l'injection intra-artérielle et intraveineuse de novacaïne. Comme méthode générale de vasodilatation provoquée par action sur l'endothélium, Progr. méd., Paris **70**:443, 1942.

PERIPHERAL-NERVE LESIONS IN HEMORRHAGIC DISEASES

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IMPAIRMENT of peripheral-nerve function as a result of hemorrhage is an incapacitating, though unusual, complication of hemorrhagic diseases. The hemorrhage may be spontaneous or may follow injury that may be slight or severe. The blood may accumulate in the tissues about the nerve, sometimes with hematoma formation, and thus injure the nerve by pressure upon it; or the bleeding may take place within the nerve sheath itself, thus injuring the fibers directly and interfering with their function. In either case serious functional impairment sometimes develops.

As is generally known, pressure of any kind upon a nerve will produce conduction defects, the degree of severity depending upon the kind and duration of pressure.[1] Tumors, aneurysms, and other growing tissue masses may have such an effect. In bleeding disorders, hemophilia, for instance, impairment of peripheral-nerve function has sometimes been associated with the presence of a hematoma adjacent to the affected nerve,[2] the severity and duration of the impairment varying directly with the degree of pressure on the nerve and the length of time it persisted. Unfortunately, however, owing to the nature of this disease and the transient character of the lesions, pathologic confirmation of an etiologic relationship of hematoma to nerve impairment is lacking.

With regard to the effect of bleeding within a nerve, it is known that functional impairment follows intraneural hemorrhage. It has been shown experimentally[3] that by the simple process of kneading a nerve intraneural hemorrhage with transi-

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2. (*a*) Aggeler, P. M., and Lucia, S. P.: Neurologic Complications of Hemophilia, J. Nerv. & Ment. Dis. **99**:475-500 (May) 1944. (*b*) Seddons, H. J.: Haemophilia as a Cause of Lesions in the Nervous System, Brain **53**:306-310 (Oct.) 1930. (*c*) Richards, R. L.: Ischaemic Lesions of Peripheral Nerves: A Review, J. Neurol., Neurosurg. & Psychiat. **14**:76-87 (May) 1951.

3. (*a*) Denny-Brown, D., and Brenner, C.: Effect of Percussion of Nerve, J. Neurol., Neurosurg. & Psychiat. **7**:76-95 (July-Oct.) 1944. (*b*) Denny-Brown, D., and Doherty, M. M.: Effects of Transient Stretching of Peripheral Nerve, Arch. Neurol. & Psychiat. **54**:116-129 (Aug.) 1945.

tory interference with function can be produced. Return of neural function occurs within a few days as the blood at the site of injury is resorbed. The presence of blood within a peripheral nerve has also been observed subsequent to various types of traumatic injury or operative manipulation,[4] stretching of a nerve,[2b] concussion of a nerve,[5] and injury by frostbite [6] or trench foot.[7] In these conditions, however, it is probable that most of the conduction defect is due to tissue injury or impaired blood supply rather than to the associated intraneural hemorrhage, which may be only incidental.

It has been suggested, however, that in some situations intraneural hemorrhage is of prime significance in the development of functional impairment despite some degree of associated trauma. Thus Stevenson [8] stated, "Some severe cases of sciatic neuritis, particularly those associated with physical strain, are partly, or even wholly, the result of hemorrhage into the nerve." Stookey [9] also thought that the overstretching of a nerve may cause intraneural hemorrhage, with residual intraneural scar formation due to the presence of blood. However, overstretching of a nerve itself may result in functional impairment as a result of direct injury of the fibers. Indeed, Denny-Brown and Doherty [2b] stated the belief that intraneural hemorrhage is of little significance in the development of nerve disorders produced by stretching. Uncomplicated hemorrhage into an organ or tissue is usually completely resorbed without fibrosis or scarring. Only when an associated inflammatory response accompanies bleeding does scarring or other permanent alteration occur. The intraneural hemorrhage produced experimentally by kneading a nerve with the fingers is resorbed within a few days without scar tissue formation. One abnormal residual alteration does remain, however, namely, local patchy demyelination in the region of kneading, which persists for a considerable period after complete resorption of the blood.[3a] Evidently, then, clear evaluation of the significance of intraneural hemorrhage in the development of neural dysfunction cannot be made when even a mild degree of direct injury of nerve fibers is present.

Nontraumatic peripheral-nerve lesions may occur in which concomitant intraneural hemorrhage is of little or no etiologic significance. Peripheral-nerve disorders, especially of the cranial nerves, have been noted in cases of leukemia,[10] and

4. (*a*) Bacsich, P., and Wyburn, G. M.: Vascular Pattern of Peripheral Nerve During Repair After Experimental Crush Injury, J. Anat. **79**:9-14 (Jan.) 1945. (*b*) Lyons, W. R., and Woodhall, B.: Atlas of Peripheral Nerve Injuries, Philadelphia, W. B. Saunders Company, 1949. (*c*) Sunderland, S.: Blood Supply of Peripheral Nerves: Practical Considerations, Arch. Neurol. & Psychiat. **54**:280-282 (Oct.) 1945.

5. Tubby, A. H.: Cases of Nerve Concussion Due to Bullet and Shell Wounds, Brit. M. J. **1**:57-59, 1915.

6. Friedman, N. B.; Lange, K., and Weiner, D.: Pathology of Experimental Frostbite, Am. J. M. Sc. **213**:61-67 (Jan.) 1947.

7. Friedman, N. B.: Pathology of Trench Foot, Am. J. Path. **21**:387-433 (May) 1945.

8. Stevenson, L.: Vascular Diseases of the Brain, in Nelson's New Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1946, Vol. 6, Chap. 7, p. 234F.

9. Stookey, B.: Surgical and Mechanical Treatment of Peripheral Nerves, Philadelphia, W. B. Saunders Company, 1922, pp. 105-106.

10. Garvey, P. H., and Lawrence, J. S.: Facial Diplegia in Lymphatic Leukemia, J. A. M. A. **101**:1941-1944 (Dec. 16) 1933. Fried, B. M.: Leukemia and the Central Nervous System, with a Review of 30 Cases from the Literature, Arch. Path. & Lab. Med. **2**:23-40, 1926.

erythrocytes, as well as leukemic cells, have been observed within the nerve. In most of these cases it was reasonably obvious that any functional impairment was due to leukemic-cell infiltration,[11] and that the presence of erythrocytes was fortuitous.

Instances of hemorrhage within a nerve with no apparent impairment of function have also been noted. In these cases there was no associated direct or traumatic injury to the nerve itself. Cottrell [12] observed erythrocytes within the perineurium of peripheral nerves of children at autopsy. It was her opinion that in this age group the cause of intraneural bleeding was probably a defect in the vessels of the perineurium.

Finally, forms of nontraumatic nerve injury may occur in which the only apparent factor responsible for the lesion is the presence of hemorrhage. For example, Hess [13] reported that in scurvy "the peripheral nerves may be the seat of hemorrhage, the blood lying between the nerve trunk and its sheath." A case of unilateral facial palsy associated with scurvy was reported by Carr.[14] He thought that the nerve impairment was due to intraneural hemorrhage.

The prolonged persistence of blood within any tissue, including a nerve, is an uncommon occurrence except in the hemorrhagic or bleeding disorders. Only in the blood dyscrasias may severe, and often persistent, bleeding occur without apparent associated mechanical or traumatic injury. Any impairment of nerve function in such a situation may then be reasonably attributed to the effects of the hemorrhage. Hence studies of the effect of uncomplicated hemorrhage on nerve function may best be demonstrated in bleeding disorders. Although hemorrhage into visceral organs has been noted in many cases of the blood dyscrasias, few instances of intraneural hemorrhage seem to have been observed.

In a few cases of hemophilia the nature and location of spontaneous hemorrhage and the associated peripheral-nerve disorder have been clinically correlated. Even in this condition, however, intraneural hemorrhage is not common and is an unlikely cause of nerve injury. Aggeler and Lucia [2a] concluded that pressure from an expanding hematoma upon an adjacent nerve was the factor responsible. They found that various nerves in both the upper and the lower extremities were involved. Curiously, and perhaps significantly, six persons had involvement of a femoral nerve. In one patient a hematoma in one thigh was associated with impairment of the (adjacent) femoral nerve; three years later, as a result of spontaneous hemorrhage in the anterior aspect of the opposite thigh, impairment of the other femoral nerve occurred. A second person had a recurrence of paralysis of the right femoral nerve one year after his first episode, and 10 years later impairment of the opposite thigh developed. However, from the very nature of this hematologic disorder, pathologic confirmation, by surgical exploration or biopsy, of a definitive relationship between hematoma and impaired nerve function is out of the question. Actually, it has also

11. Schwab, R. S., and Weiss, S.: The Neurologic Aspect of Leukemia, Am. J. M. Sc. **189**:766-778 (June) 1935.

12. Cottrell, L.: Histologic Variations with Age in Apparently Normal Peripheral Nerve Trunks, Arch. Neurol. & Psychiat. **43**:1138-1150 (June) 1940.

13. Hess, A. F.: Scurvy: Past and Present, Philadelphia, J. B. Lippincott Company, 1920, pp. 81-111.

14. Carr, J. G.: Scurvy, M. Clin. North America **5**:115-132 (July) 1921.

been suggested by Arbuse and Locascio[15] that peripheral-nerve impairment in hemophilia may be due to hemorrhage within the nerve sheath itself, rather than to external pressure from an extraneural hemorrhage.

Certain uniform clinical features characterize femoral-nerve impairment in hemophilia. There is usually a sudden onset of severe persistent aching pain in the hip on the involved side, together with a variable degree of quadriceps paralysis, loss of knee jerk, and diminution of cutaneous sensation in the region supplied by the sensory component of the nerve. In addition, tumefaction of the psoas muscle or of Scarpa's triangle is generally present. With resorption of blood a variable degree of recovery, ranging from slight to virtually complete, occurs.

The presence of hemarthrosis, with resulting crippling joint deformity, is an important cause of functional impairment of an extremity in hemophilia.[16] Consequently, permanent loss of function of an extremity is oftener the result of joint disability than of peripheral-nerve injury. Furthermore, spontaneous bleeding in hemophiliac patients may produce ischemic muscle contracture of the Volkmann type, as well as peripheral nerve injury.[17]

Although it is reasonable to believe that peripheral-nerve disorders may occur in many of the blood dyscrasias, we have been unable to locate detailed clinical reports correlating peripheral-nerve injury with spontaneous perineural or intraneural bleeding in other hemorrhagic diseases. Two cases of peripheral-nerve lesions in patients exhibiting spontaneous bleeding tendencies have recently been studied by us. In both instances the symptoms of femoral-nerve impairment resembled in many respects those found in hemophilia. One of these patients is still alive. The other, however, succumbed to his chief illness, and at necropsy the affected portion of the femoral nerve was removed for examination. The salient clinical features of both these cases are presented, together with a detailed description of the pathologic changes found in the femoral nerve of the patient who died.

INTRANEURAL HEMORRHAGE DUE TO TOXIC THROMBOCYTOPENIC PURPURA CAUSED BY PENICILLIN

CASE 1.—F. P., a white man aged 80, was brought to the hospital because of severe pain in the right hip and leg and a generalized purpuric rash on the skin. One month before admission he had been given penicillin for pneumonia, and two weeks later he had experienced sudden, severe, incapacitating pain in the right hip, generalized purpura, and painful stomatitis.

On admission, the temperature was 100 F., the pulse rate, 84, and the respiration rate, 20 per minute. The trunk and extremities were covered with innumerable, irregularly shaped, purplish hemorrhagic spots ranging from 0.1 to 10.0 cm. in greatest dimension. Several shallow ulcerated lesions were present in the mouth and on the lower gingiva. On rectal examination frank blood was found on the examining finger.

In the hospital the patient continued to suffer from constant severe aching pain in the right hip. Neurologic examination revealed no abnormality except in the right lower limb, where

15. Arbuse, D. I., and Locascio, N. R.: Neurological Manifestations in Hemophilia, M. Rec. **146**:377-381 (Nov. 3) 1937.

16. Birch, C. L.: Hemophilia: Chemical and Genetic Aspects, Illinois Medical and Dental Monographs, Urbana, University of Illinois, 1937, Vol. 1, No. 4. Davidson, C. S.; Epstein, R. D.; Miller, G. F., and Taylor, H. L.: Hemophilia: A Clinical Study of 40 Patients, Blood **4**:97-119 (Feb.) 1949.

17. Lord, J. P.: Hemophilia with Volkmann Syndrome: Report of a Case, J. A. M. A. **87**:406-407 (Aug. 7) 1929.

there was almost complete flaccid paralysis of the quadriceps femoris muscle. The knee and ankle jerks were absent on the right side, while the plantar responses were of normal flexor type. There was diminution of all sensory modalities over the anterior surface of the thigh and extending downward in a narrow band to just above the internal malleolus. This sensory impairment was strictly limited to the peripheral zone of the right femoral nerve. No essential change in these neurological findings occurred during his hospital stay.

The hemoglobin was 11.0 gm. per 100 ml.; the erythrocytes numbered 2,500,000 per cubic millimeter, and the hematocrit reading was 25. The leucocytes numbered 12,750 per cubic millimeter, with a normal differential count. The clotting time was 80% of normal. The thrombocyte count was reported as 2,000 per cubic millimeter or less on several occasions.

Because of intermittent fever, procaine penicillin G was again given. An exacerbation of the bleeding tendency occurred, and administration of this agent was discontinued after five days because it was thought that it might be responsible for the patient's bleeding tendency.

A diagnosis of secondary thrombocytopenic purpura due to an abnormal reaction to penicillin was made. Although removal of the spleen was not recommended, this procedure was nevertheless performed as a last resort because his disability was becoming rapidly and progressively worse. A transient rise in the thrombocyte count followed splenectomy, and the bleeding tendency diminished. Soon thereafter, however, the thrombocytes began to fall steadily, and three weeks after operation none at all could be found in the peripheral blood.

Two days before he died, he fell and sustained a small laceration over the occipital region of the scalp. After this injury he became drowsy and comatose and died 80 days after the onset of his first symptoms.

An autopsy was performed 10 hours after death. The pertinent findings follow. The skin of the entire body was covered with multitudinous irregular, purple ecchymoses. A recent superficial laceration, about which the subcutaneous tissues were diffusely hemorrhagic, was present over the left occipital area. A large hematoma was present in the splenic bed, and the tissues about this operative site were suffused with blood. Many of the viscera were focally hemorrhagic. Numerous small subarachnoid hemorrhages, ranging from 0.5 to 2.0 cm. in size, were seen over the cerebral hemispheres. Diffuse hemorrhages into the cerebral tissues and basal ganglia were also noted. The ventricular system of the brain was symmetrically dilated and filled with fresh blood. It was thought that the intracerebral hemorrhage was the immediate cause of death.

The right femoral nerve, when exposed in the pelvis, was found to contain an intraneural hemorrhage 1 cm. in length, located approximately 3 cm. distal to the junction of the third and fourth lumbar roots. No evidence of hemorrhage was observed in the surrounding psoas muscle, nor was there any extraneural hematoma or other mass pressing upon the nerve. The pelvic segment of this nerve was removed *in toto* and fixed in 10% formalin solution for 24 hours.

Serial sections from the hemorrhagic portion of the nerve were made and stained by a variety of techniques. The erythrocytes in the hemorrhagic focus were best visualized by means of Mallory's phosphotungstic acid-hematoxylin stain, which imparted a deep-blue color to the red blood corpuscles while the surrounding tissues were stained light-brown.

The hemorrhage was most extensive just beneath the perineurium in 4 of 19 fascicles. No erythrocytes were present in the epineurium. The greatest degree of bleeding had occurred in the loose connective tissue space between perineurium and endoneurium. In some instances separation of the endoneurial tissues by erythrocytes was also observed, as well as slight separation of the nerve fibers themselves. While no acute inflammatory response was present, macrophages containing hemosiderin pigment were seen, indicating that erythrocytes had been present for several days. A Weil-Weigert stain revealed the presence of patchy demyelination of nerve sheaths in the region of hemorrhage. No evidence of demyelination of axis-cylinders at a distance of 1 cm. or more distal to the hemorrhage was observed, indicating that there was no degeneration of the Wallerian type. Sections stained by Mallory's eosin-methylene blue method and by Bodian's technique showed no evidence of disruption of axis-cylinders either in the region of hemorrhage or distal to it.

Serial sections of the nerve in the hemorrhagic zones revealed the presence of rupture of a capillary channel within the perineurium of two of the four fascicles that contained erythrocytes. The sites of rupture appeared just beneath the perineurium, within the space between perineurium and endoneurium. In each instance this space was distended and filled with blood.

Comment.—A wide variety of side-reactions have occurred subsequent to the administration of penicillin,[18] the majority of which are rashes, urticarias, and similar lesions, which could hardly be considered serious. Purpuric reactions are uncommon,[19] and toxic or secondary thrombocytopenic purpura is decidedly rare. Furthermore, only a few deaths are alleged to have resulted primarily from the

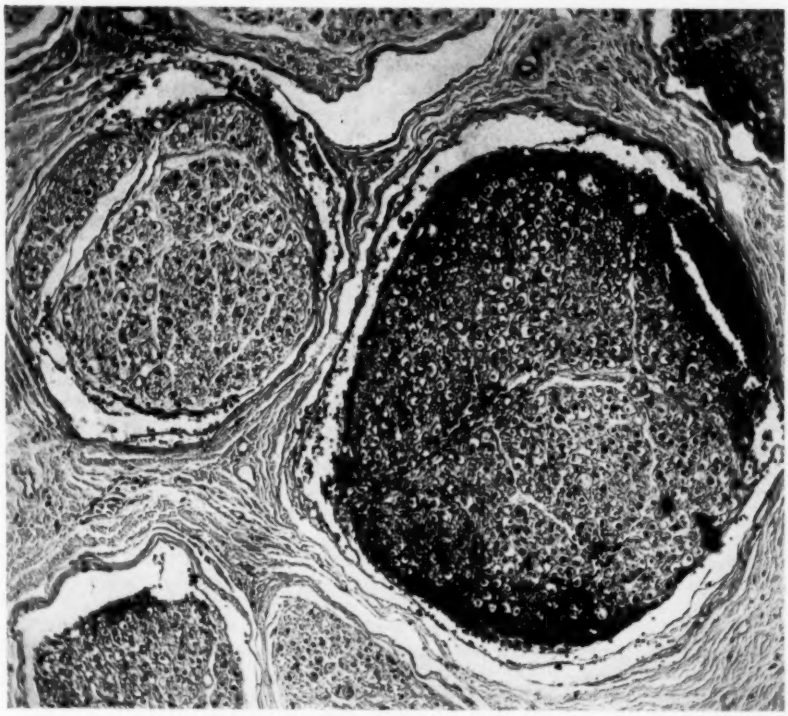

Fig. 1.—Cross section of the femoral nerve revealing the presence of blood in four fascicles. The erythrocytes are most numerous in the space between the perineurium and the endoneurium, although some extension into the endoneurium is also present. Phosphotungstic acid-hematoxylin stain; × 125.

18. Morginson, W. J.: Toxic Reactions Accompanying Penicillin Therapy, J. A. M. A. **132**:915-919 (Dec. 14) 1946.

19. Brown, E. A.: Progress in Allergy: Reactions to Penicillin; a Review of the Literature 1943-1948, Ann. Allergy **6**:723-746 (Nov.-Dec.) 1948. Price, I. C.: Severe Allergic Reaction to Intramuscular Penicillin, Canad. M. A. J. **53**:485-486 (Nov.) 1945. Anderson, A. B.: Anaphylactic Purpura Following Intramuscular Penicillin Therapy, M. J. Australia **1**:305-306 (March 8) 1947. Spring, M.: Purpura and Nephritis After Administration of Procaine Penicillin, J. A. M. A. **147**:1139-1141 (Nov. 17) 1951. Pillsbury, D. M.; Steiger, H. P., and Gibson, T. E.: Management of Urticaria Due to Penicillin, J. A. M. A. **133**:1255-1258 (April 26) 1947.

administration of penicillin.[20] In this case the development of the thrombocytopenic purpura, which terminated fatally, apparently resulted from a toxic reaction to penicillin.

From a careful study of the affected tissues, we believe that the impairment of the femoral nerve was due solely to hemorrhage within the nerve sheath. Moreover, we believe that such a paralysis could also have resulted from spontaneous intraneural hemorrhage associated with any form of hemorrhagic disease.

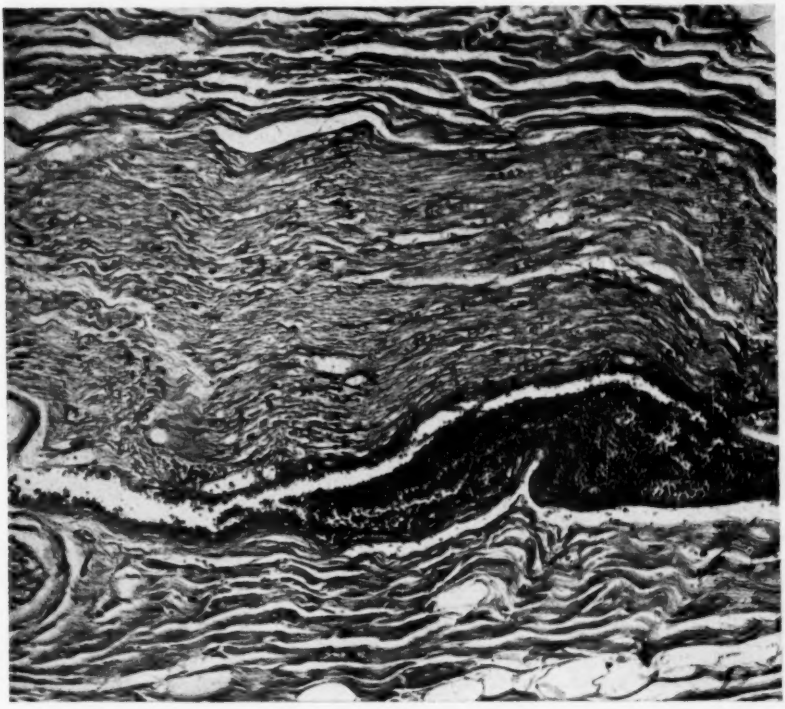

Fig. 2.—Longitudinal section of the femoral nerve showing hemorrhage within the perineurial and endoneurial spaces. Phosphotungstic acid-hematoxylin stain; × 130.

Two factors are generally considered responsible for the bleeding tendency in thrombocytopenic purpura, namely, some form of capillary defect and a reduction in the number of thrombocytes.[21] The latter abnormality is considered of less importance, since purpuras of the nonthrombopenic type are well known. The vasa

20. Flaxman, N.: Drug Fatalities, J. A. M. A. **137**:377-380 (Sept. 29) 1951.

21. Wiseman, B. K.; Doan, C. A., and Wilson, S. J.: Present Status of Thrombocytopenic Purpura, with Special Reference to Diagnosis and Treatment, J. A. M. A. **115**:8-13 (July 6) 1940. Ackroyd, J. F.: Pathogenesis of Thrombocytopenic Purpura Due to Hypersensitivity to Sedormid (Allyl-Isopropyl-Acetyl-Carbamide), Clin. Sc. **7**:249-285 (April) 1949.

nervorum are composed of anastomosing vascular channels which form a plexus within the peripheral nerve. The small arteries and arterioles constantly subdivide into smaller and smaller channels. As a result of this vascular branching, the blood supply of the perineurium and of the structures within it, consisting of endoneurium, neurilemmal sheaths, myelin sheaths, and axis-cylinders, is provided chiefly by precapillaries and capillaries.[22] It is precisely these structures which are defective

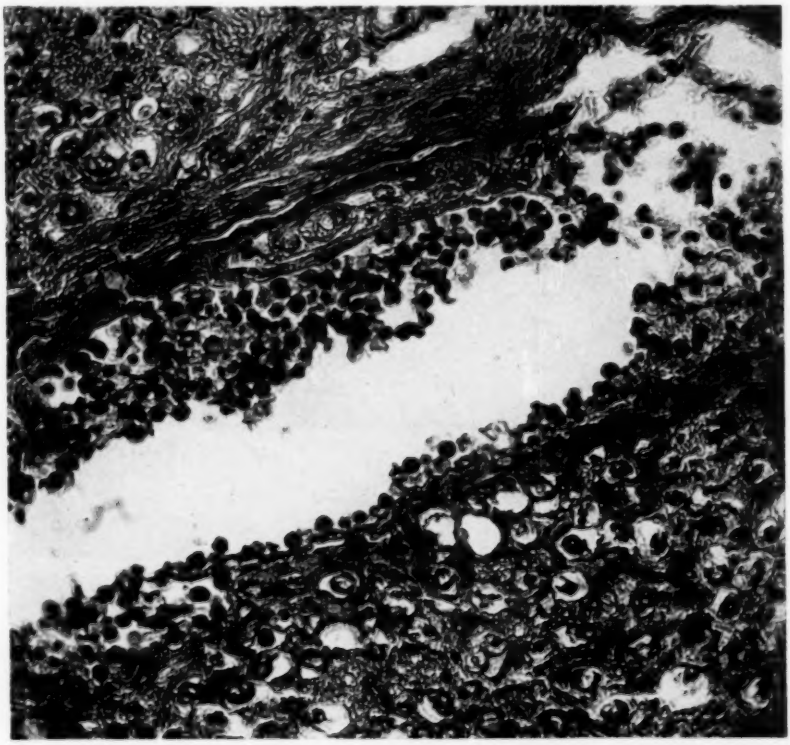

Fig. 3.—Small precapillary vessel, on the inner margin of the perineurium, showing rupture of its wall. Blood is present in the perineurial and endoneurial spaces. Phosphotungstic acid-hematoxylin stain; × 550.

in thrombocytopenic purpura and are the vessels most subject to rupture, with resulting hemorrhage.

Humble [23] believes that at least in the skin, and presumably elsewhere, the site of capillary hemorrhage in purpuric diseases is localized at the arteriolar end of

22. Bacsich, P., and Wyburn, G. M.[4a] Sunderland, S.: Blood Supply of the Nerves of the Upper Limb in Man, Arch. Neurol. & Psychiat. **53**:91-115 (Feb.) 1945. (*c*) Adams, W. E.: Blood Supply of Nerves: I. Historical Review, J. Anat. **76**:323-341 (July) 1942.

23. Humble, J. G.: Mechanisms of Petechial Hemorrhage Formation, Blood **4**:69-75 (Jan.) 1949.

the capillary loop. It is not surprising, therefore, that intraneural hemorrhage should occur, as it did in our case, within the fascicles of the nerve, and not in the epineurial structures. Local ischemia or pressure from the interstitial accumulations of blood was presumably responsible for demyelination of nerve sheath at the site of hemorrhage; for localized demyelinating lesions in a peripheral nerve, without associated Wallerian degeneration, have been described at sites of transient localized ischemia or pressure.[3b]

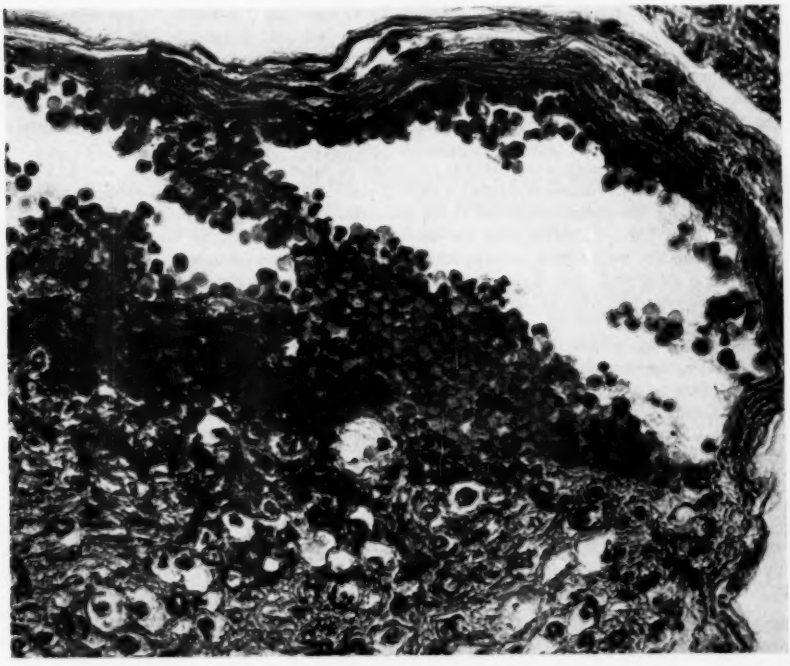

Fig. 4.—Section of nerve showing marked distention of the perineurial space by blood. Penetration and partial disruption of the endoneurium are also observed. Phosphotungstic acid-hematoxylin stain; × 550.

Although the intraneural hemorrhage described is considered to be a sufficient explanation of the femoral-nerve disability suffered by this man, it may not have been the only factor responsible. A few reports have recorded peripheral-nerve disability or paralysis which developed after penicillin therapy, presumably without evidence of local intraneural hemorrhage.[24] However, in none of these other cases were the affected tissues subjected to histologic study.

24. Kolb, L. C., and Gray, S. J.: Peripheral Neuritis as a Complication of Penicillin Therapy, J. A. M. A. **132**:323-326 (Oct. 12) 1946. Barksdale, E. E., in discussion on Morginson.[18]

FEMORAL NEUROPATHY IN PRIMARY HEMORRHAGIC THROMBOCYTHEMIA

CASE 2.—A. F., a white man aged 40, was first admitted to the hospital because of continuous pain and disability of the right hip following a fall while roller-skating six months previously. The pain had been of sudden onset, occurring almost immediately after the fall. Soon thereafter, a large hematoma developed over the anterior aspect of the right thigh and hip. In the few months prior to admission other hematomata had appeared as a result of seemingly insignificant traumas. During the six months' interval following this fall the pain in the right hip had persisted and increased in severity. It was aggravated by walking and partially alleviated by rest.

Neurologic examination showed a normal condition except for the right lower extremity. The right thigh was held in a flexed position. There was flaccid paralysis of the right quadriceps femoris muscle without atrophy. The right knee jerk was absent; the left knee jerk was 2+, and both ankle jerks were 2+. Babinski's sign was not elicited in either extremity. There were hypalgesia and hypesthesia over the anterior surface of the right thigh and extending downward over the inner aspect of the leg to the internal malleolus; this area of sensory loss was limited to the sensory distribution of the femoral nerve. A firm, tender mass was palpable in the right thigh over the femoral triangle.

The thrombocyte count was 3,500,000 per cubic millimeter. The hemoglobin was 12.5 gm. per 100 ml.; the erythrocytes numbered 4,100,000 per cubic millimeter; the hematocrit reading was 42, and the leucocytes numbered 11,150 per cubic millimeter. The prothrombin time was 8% of normal. The coagulation time was four minutes and the bleeding time one-half minute, both values being well within normal limits. Clot retraction was normal. Aspiration biopsy specimens from several sites of the sternal marrow revealed a marked increase in thrombocytes and megakaryocytes without any hyperplasia of the granulocytopoietic or erythropoietic elements.

The patient was considered to have primary hemorrhagic thrombocythemia. After x-irradiation therapy, the thrombocyte count decreased. The bleeding tendency subsided and had not recurred nine months later. While some residual atrophy of the thigh remained, there was approximately 75% recovery of motor and sensory function. The hematoma of the thigh resolved. Unfortunately, the patient moved to another part of the country, and further clinical studies could not be made.

Comment.—The bleeding tendency in the second case resulted from a rare hematologic condition which has been designated by various terms, of which primary hemorrhagic thrombocythemia seems most apt. Less than a dozen cases of this condition have been described.[25] It is known that an elevated thrombocyte count may be present in various disorders, such as chronic leukemia, postsplenectomy status, or polycythemia vera. In this condition, bleeding tendencies occur in association with a marked elevation of the thrombocyte count. An explanation for the elevation of thrombocytes is lacking. This case, except for the greatly reduced prothrombin time, is similar in most respects to those which have been reported. As far as we know, a decreased prothrombin time in primary hemorrhagic thrombocythemia has not previously been recorded. It is noteworthy also that Holst's [25a] patient with this disease likewise suffered from a neurologic complication, hematomyelia, presumably as a result of the bleeding tendency.

In Case 2, the term "spontaneous" is used in the sense that the degree and severity of the hemorrhage that occurred seemed out of all proportion to the injury sustained by the patient when he fell. The nerve disability itself may have been the result of external pressure upon the nerve; the hematoma in the anterior aspect of the right thigh, enclosed, as it would be, within fascial planes, could exert a

25. (*a*) Holst, J. E.: Hemorrhagical Thrombocythemia, Acta med. scandinav. **13**:507-514, 1948. (*b*) Jasinski, B.: Zur Pathogenese der Thrombocythämie, Acta haemat. **2**:145-152, 1949.

sufficient degree of pressure upon the nerve to cause functional impairment. The clinical neurologic pattern is remarkably similar to the femoral paralysis that has occurred in cases of hemophilia. The possibility also exists, of course, that intraneural hemorrhage may have been responsible for the nerve lesion, as in Case 1.

COMMENT

Intracranial and intraspinal hemorrhages are well-recognized complications of hemorrhagic diseases and have been reported in a wide variety of blood dyscrasias, including hemophilia,[26b] leukemia,[26] thrombocytopenic purpura,[27] parahemophilia,[28] afibrinoginemia,[29] childhood anemias,[30] Hodgkin's disease,[30] vitamin-K deficiency,[31] and idiopathic hypoprothrombinemia.[32] It is also recognized that intracranial hemorrhage in these disorders may sometimes be the immediate cause of death. In fact, Garvey and Stephens [27a] maintained that bleeding within the cranium is the commonest cause of death in thrombocytopenia purpura, as in Case 1.

Peripheral-nerve lesions as a result of hemorrhage within the nerve, or outside it and pressing upon it, seem to be far less common, if the scarcity of reports is any indication of their frequency. It is our belief, though, that consideration of the hematologic disorder may overshadow adequate evaluation of peripheral-nerve lesions in many instances.

Opportunities to evaluate more fully the pathologic changes due to hemorrhage within or about a nerve sheath are necessarily limited. The nature of the hemorrhagic disease itself usually precluded surgical intervention, such as the obtaining of a biopsy specimen. Moreover, the removal of a segment of a large nerve from a living subject is not feasible. An amputated extremity, or the organs available at autopsy, permit more detailed study. Unfortunately, however, examination and removal of peripheral nerves are not generally done at routine autopsies. Hence it is important that careful note be made to ascertain which nerves should be observed and removed for subsequent examination in cases of hemorrhagic disease. Actually, clinical recognition of peripheral-nerve injuries due to bleeding should be easy. In instances in which nerves containing both motor and sensory fibers are involved, particularly the femoral nerve, an incapacitating degree of constant aching pain

26. (*a*) Diamond, I. B.: Leukemic Changes in the Brain: A Report of 14 Cases, Arch. Neurol. & Psychiat. **32**:118-142 (July) 1934. (*b*) Critchley, M., and Greenfield, J. G.: Spinal Symptoms in Chloroma and Leukaemia, Brain **53**:11-37 (April) 1930.

27. (*a*) Garvey, P. H., and Stephens, D. J.: Purpura Hemorrhagica with Intracranial Hemorrhage, New York J. Med. **36**:97-101 (Jan. 15) 1936. (*b*) Olsen, C. W., and Comstock, D. D.: Purpura Hemorrhagica Complicated by Hematomyelia: Report of Case, Bull. Los Angeles Neurol. Soc. **2**:135-140 (Sept.) 1937.

28. Minot, G. R.: A Familial Hemorrhagic Condition Associated with Prolongation of the Bleeding Time, Am. J. M. Sc. **175**:301-306 (March) 1928.

29. Schönholzer, cited by Quick, A. J.: Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942.

30. Sheldon, W. P. H.: Intracranial Hemorrhage in Infancy and Childhood, Quart. J. Med. **20**:353-370 (July) 1927.

31. Grossman, A. M.: Coagulation Defects in Infancy and Childhood: The Frequency of Hypoprothrombinemic States and Their Treatment with Vitamin K.; a Reclassification of Hemorrhagica Hypoprothrombinemia Neonatorum, J. Pediat. **19**:205-217 (Aug.) 1941.

32. Rhoads, J. E., and Fitz-Hugh, T.: Idiopathic Hypoprothrombinemia: An Apparently Unrecorded Condition, Am. J. M. Sc. **202**:662-670 (Nov.) 1941.

appears to be the prime clinical feature. The associated muscular weakness and sensory loss are of only secondary concern to the patient, at least while the pain persists. With resorption of the hemorrhage, pain subsides, and there is return of much, if not all, of the function.

SUMMARY

The occurrence and significance of lesions of peripheral nerves in hemorrhagic diseases are discussed. Two cases are presented. In one of these cases there were impairment of femoral-nerve function and associated spontaneous hemorrhage within the nerve, presumably as a result of secondary thrombocytopenic purpura produced by the administration of penicillin. In the other, peripheral-nerve injury apparently resulted from the pressure effects of a hematoma impinging upon the nerve. The latter patient had a rare blood dyscrasia, primary hemorrhagic thrombocythemia.

INCIDENCE OF EPILEPSY FOLLOWING CRANIOCEREBRAL INJURY

II. Three-Year Follow-up Study

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BOSTON

THE ULTIMATE total incidence of epilepsy following craniocerebral injury remains to be determined. It will be partly dependent on the time elapsed since injury and the validity of the methods employed in the detection of posttraumatic epilepsy. The evaluation of such factors as number of patients examined, methods of examination and follow-up observation, definition of the terms "head injury" and "epilepsy," criteria for diagnosis of epilepsy, and recognition and separation of "late epilepsy" and "early epilepsy" has been undertaken previously by me,[1] as well as by Denny-Brown,[2] Elvidge,[3] and Walker.[4] The present study deals with the incidence of "late epilepsy," three years after injury to the brain in healthy young men as the result of projectile damage to the scalp, skull, dura, and brain. The material and methods are identical with those employed in my previous examination of incidence two years after injury.[1] In addition, data relating to persistence of seizures are now examined.

MATERIALS AND METHODS

The present study represents the results of a detailed questionnaire with appropriate verifications sent to 500 otherwise healthy men who had seen active military combat service.[1] Of the original group, 286 were studied in detail. These were unselected with respect to severity, location, and condition of their head wounds. All the 286 men were known to have sustained a "penetrating head injury." Detailed questionnaires designed to determine the patient's condition three years after the original wound were submitted to the 500 patients. Construction of the questionnaires was such as to minimize error. Two hundred eighty-six persons furnished replies satisfactory for analysis. The raw data were examined critically; ambiguous responses were rejected or clarified by renewed questioning of the patients and/or relatives. Replies obtained were compared with replies submitted a year earlier. The data were recorded on

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1. Watson, C. W.: Incidence of Epilepsy Following Cranio-Cerebral Injury, A. Res. Nerv. & Ment. Dis., Proc. **26**:516-528, 1947.

2. Denny-Brown, D.: Clinical Aspects of Traumatic Epilepsy, Am. J. Psychiat. **100**:585-592, 1944.

3. Elvidge, A. R.: The Post-Traumatic Convulsive and Allied States, in Brock, S., Editor: Injuries of the Skull, Brain and Spinal Cord, Ed. 2, Baltimore, Williams & Wilkins Company, 1940, pp. 233-273.

4. Walker, A. E.: Posttraumatic Epilepsy, Springfield, Ill., Charles C Thomas, Publisher, 1948.

punch cards bearing the original data relative to history, neurological examinations, operative reports, electroencephalographic and roentgenographic examinations, and follow-up studies. This permitted cross checking for validity of replies.

It is particularly emphasized that the patients in whom epilepsy developed within the first four weeks after injury were excluded unless the seizures persisted. As previously, the area of inquiry is confined to the incidence of "late post-traumatic epilepsy" in persons with evidence of cerebral damage.

GENERAL INCIDENCE

Subject to the conditions outlined above, the over-all incidence of all types of epilepsy is summarized in Table 1.

PROGNOSIS

Table 2 summarizes the findings relating to persistence of seizures in 53 patients, irrespective of medication, although, with few exceptions, affected persons were

TABLE 1.—*General Incidence of Post-Traumatic Epilepsy in Patients with Craniocerebral Injury*

Elapsed Time Since Injury	Two Years		Three Years	
	No.	Percentage	No.	Percentage
Patients questioned	500	....	500	....
Replies satisfactory for analysis	279	....	286	....
Patients with seizures	101	36.2	119	41.6

TABLE 2.—*Persistence of Post-Traumatic Epilepsy Three Years After Injury*

	No.	Percentage
Epileptic patients questioned	126	....
Replies satisfactory for analysis relative to persistence of seizures	53	....
Patients free of seizures one year or more	9	17.0
Patients continuing to have seizures	44	83.0
Improved	20	37.8
Unchanged	9	17.0
Worse	15	28.2

taking diphenylhydantoin (dilantin®) and/or phenobarbital. Persons were counted as "free of seizures" when none had occurred for one year or more. Improvement or worsening was judged on the basis of frequency and/or severity of seizures or change to a type of more or less disagreeable character.

Thus, four-fifths of this group of 53 persons continued to have seizures three years after injury, even though the majority were receiving anticonvulsant medication. Although the group is small and the adequacy of medication is unknown, this low recovery rate is in close accord with the findings of Alström.[5]

The incidence of epilepsy with relation to the area of brain injury was not significantly different from that previously reported[1]; nor was there any significant change from the previous study in the statistical distribution of clinical manifestations or mortality incidence.

5. Alström, C. H.: Study of Epilepsy in Its Clinical, Social and Genetic Aspects, Copenhagen, Ejnar Munksgaards Forlag, 1950.

COMMENT

These data are in accord with the prevailing view that the most likely time for seizures to develop is within the first two years after original injury [5]; nevertheless, 18 additional patients had onset of seizures during the third year, raising the total incidence to 41.6%.

If the reports of other investigators are reviewed critically, it is apparent that those who have carefully considered the problems of accurate diagnosis of epilepsy, accurate localization of the wound, necessity for exclusion of "early epilepsy," and, in particular, establishment of the fact of damage to brain substance are in agreement that the ultimate incidence, regardless of site, exceeds 40%.[6] Rawling [7] and Steinthal and Nagel [8] found the general incidence to exceed 30%. There are a multitude of reasons for the difference in incidence as determined by different authors. The inclusion of "early epilepsy" is likely to raise the figure artificially, as is the inclusion as epilepsy of such debatable symptoms as paroxysmal unilateral headache, slight vertigo, abdominal pain, clonus associated with spastic hemiplegia, or vague scotomas. These and other poorly defined phenomena have been excluded in this study. On the other hand, some epileptic phenomena may be entirely overlooked by the patient and become evident only on direct questioning. One such patient, a left-handed person with gunshot wound in the right occipital region, experienced paroxysmal left homonymous hemianopsia, followed by paroxysmal aphasia and a right-sided Jacksonian sensory "march." The figure is likely to be artificially low if the patients are not personally known to the investigator, if any nonpenetrating injuries are included, if true minor seizures in the visual or tactile spheres are ignored, if the questionnaire method is used without careful construction in conjunction with a cumulative recording system to permit cross checking of result, if too large a series of patients are examined and if the incidence is calculated without accurate firsthand knowledge of the original number of penetrating head injuries from which a known number of epileptics is derived.

I found no evidence of hereditary predisposition as judged by a high relative incidence of epileptic relatives among the affected patients,[1] and in this I am in agreement with Quadfasel and Walker.[9] Indeed, Alström,[5] in a careful study of 897 proband families, found that the average over-all incidence of epilepsy (mixed causes) among close relatives was 1.5%, and that it did not significantly exceed that of the general population. Thus, even for epilepsy of undesignated cause the data derived from relatives failed to support a genetic hypothesis for the group as a whole.

Evidence from other sources confirms the remarkable degree of liability to epilepsy of the average person.[10] Thus, epilepsy occurs in 87.5% of persons with

6. Ascroft, P. B.: Traumatic Epilepsy After Gunshot Wound of the Head, Brit. M. J. **1**:739-744, 1941. Credner, L.: Klinische und soziale Auswirkungen von Hirnschädigungen, Ztschr. ges. Neurol. u. Psychiat. **126**:721-757, 1930.

7. Rawling, L. B.: Remote Effects of Gunshot Wounds of the Head, Brit. J. Surg. **10**:93-126, 1922.

8. Steinthal, K., and Nagel, H.: Die Leistungsfähigkeit im bürgerlichen Beruf nach Hirnschüssen mit besonderer Berücksichtigung der traumatischen Epilepsie, Beitr. klin. Chir. **137**:361-400, 1926.

9. Quadfasel, F. A., and Walker, A. E.: Problems of Post-Traumatic Epilepsy in an Army General Hospital, A. Res. Nerv. & Ment. Dis., Proc. **26**:461-475, 1947.

10. Watson, C. W.: Epilepsy, Am. J. Psychiat. **108**:533-534, 1952.

globular parasagittal meningiomas of the central third of the falx [11] and in virtually all persons with cerebral cystocercosis.[2] These data suggest that "predisposition," termed hereditary, does not play a significant role in symptomatic epilepsy.

The interval between the injury and the first recognized seizure may be as long as two decades; hence the ultimate incidence is not yet at a maximum for the group. Meyer [12] described 33 cases of gunshot wounds of the head in which seizures developed only after eight or more years had intervened.

SUMMARY

The incidence of epilepsy three years after penetrating head injuries among 286 healthy young adults was found to be 41.6%.

Eighty-three per cent of patients continued to have seizures three years after injury.

Factors affecting the incidence of post-traumatic epilepsy and its determination are discussed.

Neurological Unit, Boston City Hospital.

11. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938, pp. 359-387.

12. Meyer, W. C.: Late Post-Traumatic Epilepsy, Ztschr. Nervenh. **139**:278-293, 1936.

SLEEP PARALYSIS SUCCESSFULLY TREATED WITH INSULIN HYPOGLYCEMIA

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SLEEP paralysis is a disturbance of the process of awakening from sleep in which the conscious sensory phase is followed by a prolonged delay in the ability to move, during which the voluntary muscles are temporarily paralyzed. It is an entity which is not often encountered [1] and for which heretofore there has been no treatment beyond reassurance. For these reasons, the following case report and record of successful treatment with mild insulin hypoglycemia are submitted. This treatment also has implications for a therapeutic approach to other disorders of possible hypothalamic origin.

METHOD OF TREATMENT

The patient, who was in an overnight fasting state, was given regular insulin intramuscularly at the medical clinic office. The dose was so adjusted as to produce a mild hypoglycemic reaction, as shown by mild sweating, within 1 to 1¼ hours. This reaction was at once counteracted by the ingestion of 12 oz. (360 cc.) of orange juice, two meat sandwiches, and 1 pint (500 cc.) of milk. Further feeding at home prevented additional reactions. The patient was treated every second day for the first two weeks. The intervals between treatment days were increased by one day every two weeks, so that by the 9th and 10th weeks he was treated every seventh day. The dose of insulin used was 20 to 25 units. Four grams of ascorbic acid was given orally each day in divided doses (probably unnecessarily) in order to protect the adrenal glands from exhaustion, as well as to insure the presence of possible precursors of adrenocortical hormones.[2]

From the Department of Medicine, Permanente Foundation Hospital.

1. Brain, W. R.: Sleep: Normal and Pathological, Brit. M. J. **2**:51-53 (July 8) 1939. Lichtenstein, B. W., and Rosenblum, A. H.: Sleep Paralysis, J. Nerv. & Ment. Dis. **95**:153-155 (Feb.) 1942. Hadley, H. F.: Narcolepsy, M. Rec. **155**:211-212 (March 18) 1942. Levin, M.: Diplopia in Narcolepsy, Arch. Ophth. **29**:942-955 (June) 1943. Rushton, J. G.: Sleep Paralysis: Report of 2 Cases, Proc. Staff Meet., Mayo Clin. **19**:51 (Jan. 26) 1944; Sleep Paralysis, M. Clin. North America **28**:945-949 (July) 1944. Levin, M.: Military Aspects of Narcolepsy, War Med. **6**:162-165 (Sept.) 1944. Chodoff, P.: Sleep Paralysis, with Report of 2 Cases, J. Nerv. & Ment. Dis. **100**:278-281 (Sept.) 1944. Harper, F. T.: Narcolepsy, with Report of 4 Cases, North Carolina M. J. **6**:96-98 (Feb.) 1945. Van der Heide, C., and Weinberg, J.: Sleep Paralysis and Combat Fatigue, Psychosom. Med. **7**:330-334 (Nov.) 1945. Fabing, H. D.: Narcolepsy: I. Combat Experience of a Soldier with Narcolepsy; II. Theory of Pathogenesis of the Narcolepsy-Cataplexy Syndrome, Arch. Neurol. & Psychiat. **54**:367-371 (Nov.) 1945; **55**:353-363 (April) 1946. Murphy, G.: Sleep Paralysis: Report of 2 Cases, Prensa méd. argent. **34**:2061-2064 (Oct. 24) 1947. Vaisrub, S.: Nocturnal Disorders of Medical Interest, Ann. Int. Med. **35**:323-330 (Aug.) 1950. Schreck, J. W.: Sleep Paralysis, Am. J. Psychiat. **108**:921-923 (June) 1952.

2. Beck, J. C.; Browne, J. S. L., and Mackenzie, K. R.: Effect of Adrenocorticotrophic Hormone and Cortisone Acetate on the Metabolism of Ascorbic Acid, Proceedings Second Clinical ACTH Conference, Editor, J. R. Mote, New York, The Blakiston Company, 1951, Vol. 1, p. 355.

REPORT OF A CASE

E. T., a 55-year-old Negro, was referred with the sole complaint of "strong dreams which awakened him frequently from sleep, and paralysis on awakening."

The patient had noted his first attack of sleep paralysis 10 years prior to consultation. Since then, these attacks had occurred from one to four times in a night and one to seven nights in a week. Recently, the attacks had been almost nightly. As the patient remarked, "I'm lucky there are no more than seven nights in each week."

The longest continuous span of time during the past 10 years in which he was free from any attack of sleep paralysis was 2½ weeks, this interval having been five years before. Except for that single occasion, the greatest respite from any attack of sleep paralysis was an occasional week.

A typical attack was reconstructed by the patient as follows: After the patient had fallen asleep normally at his accustomed hour, he would gradually awaken after a variable period. At a moment at which he would feel himself to be awake all attempts to stir would fail. He could not alter the recumbent and curved passivity of his body as it lay at random position. He knew that he was once more going through an attack of paralysis. A sense of generalized tingling was felt, increasing as the attack developed. He was conscious of the passage of time. Voices and other sounds were easily recognized and were extraordinarily loud and clear. He strained to cry out for help but was unable to utter a sound. Although he sensed the presence of others who were close by, he felt himself to be overwhelmingly isolated as he failed in every effort to contact them. A fear of paralysis impelled him to struggle for movement. He could recall the other attacks that had occurred. They were as real as daily train rides down a steep grade. The previous attacks had always ended safely. Yet during each attack he felt uncertain of the outcome. He wondered what would happen in the event that the paralysis would be prolonged beyond precedent. He suspected that an indefinite extension of paralysis might easily occur, and that he might in all helplessness drift into death unless he concentrated upon nothing else than the struggle to break out of his immobility. He knew that this attack would be terminated as soon as he could move any portion of his own body, or else whenever someone touched him. Although he intensified his efforts to break out of his encasement, his continued paralysis was terrifying. He seemed to become less effective, although the increasing sensation of generalized tingling had always presaged the closing moments. A slight motion of his large toe broke the attack. His recovery was abrupt. All his muscle power was instantly restored to normal. He rolled over, sat up, stretched, moved around to test himself for normal recovery, and then returned to bed for a resumption of normal sleep.

These attacks were of a constant pattern, having changed only in frequency and duration since they were first noticed, 10 years before. During the course of any given attack the following components were invariably present: 1. The attack occurred only during the night. 2. A period of natural sleep was present prior to the attack. 3. There was a sensory consciousness of being fully awake. Sight (light or darkness), hearing, touch, position of his limbs, and orientation in time and space were all present, and even exaggerated. Thus, the clock ticking in the kitchen was loud. A passing automobile in a distant street seemed to pass directly below his room. A dog in the yard stepped on a twig; it cracked sharply. The touch of his bedclothes was distinctly felt. Apparently, it was not the sense of touch in itself that could terminate the attack, but a changing touch such as that by someone else. He knew exactly how his body was sloped and curved, whether his posture was to one side or face down; but in every instance he would discover this posture without being able to alter it. He was oriented realistically as to where he was, in what direction he was facing, and what time of the night it was. He could account for the passage of time with great accuracy, sometimes counting off the seconds. There was never any false aura of sensory orientation. After each attack there was complete continuity between the experiences during and after each attack. As far as the patient could describe, he felt that in all respects he was as awake during the attack as after its termination, except for motion. 4. The paralysis of voluntary muscles was complete, including the muscles responsible for speech. 5. The restoration of muscle power occurred instantaneously and was complete, including those of speech. 6. The paralysis could be terminated in a moment if someone were to touch him. A very light momentary touch was sufficient to abolish the attack immediately.

7. The duration of the attack was otherwise self-limited. The duration of the attack varied only between a maximum and a minimum time limit. As estimated by the patient, it rarely lasted more than 10 minutes and was never less than 3 minutes. For the past two years the attacks were frequently of 10 minutes' duration, with the time for all attacks averaging about 6 minutes. There had been a gradual increase in the duration of each attack during the past 10 years. Initially the average attack lasted two minutes. 8. The quality of the entire attack was vivid. Upon recovering from each attack of sleep paralysis, the patient could recall his experiences during the attack. Its terrifying impact was remembered for days to years after each occurrence. 9. Shortly before the attack was terminated he noticed a rapid and forceful pounding of his heart, which lasted one minute after motion, when the heart returned to its accustomed rhythm.

The attacks were distinct from dreams. When the attacks were associated with dreams, the dreams preceded the paralysis. The dreams gradually merged with the conscious state, but tended to remain as an unreal feature for only the first portion of the paralysis. This gave rise to bizarre nocturnal experiences, which were terrifying to the patient, during the initial phase of the attack. On one occasion he dreamt that a dog was chasing him but that he could not escape from the dog because he was unable to run. This dream gradually merged into an attack of sleep paralysis that lasted for about 10 minutes. The vicious beast continued to menace him. The patient became aware that he was in sleep paralysis, awake but completely paralyzed, with a ferocious animal straining at him. He was able to tell himself that the dog was only a dream, as separate from the "real" paralysis. After the termination of this episode, he was able to differentiate between the "ordinary dream" and the attack of sleep paralysis. Thus, he could not recall parts of the preliminary dream, such as how the dog got there in the first place, but he was able to recall the entire period of the sleep-paralysis attack, including the knowledge of when the dream ended and when it merged with the sleep paralysis. Furthermore, the sensations associated with the sleep paralysis were much more powerful than those associated with the nightmare type of dream. He was unable to estimate the passing of time in ordinary dreams, but he was usually certain of the measured amount of time of the sleep-paralysis attack. Qualitatively, this sense of time which was present during the sleep-paralysis attack was modified by the seemingly interminable passage of time, which was at the most a 10-minute period, during which he fought desperately to call out and to break through his paralysis.

The attending circumstances surrounding each attack were as follows: One attack of sleep paralysis tended to be followed by others during the same night. On frequent occasions as many as four attacks occurred in a night. Each attack was similar to the others in quality and in the duration of the paralysis. However, whenever an attack of sleep paralysis was preceded by a dream, the subsequent attacks of sleep paralysis were not accompanied by the same dream. During each of his attacks of sleep paralysis, the patient was able to sense the development of the attack without being able to prevent or to alter the inevitable unfolding of its progress. He would know that the attack of sleep paralysis was upon him because he would feel awake. Somehow, he could recall having passed through this episode on innumerable occasions. He was conscious of the presence of others around him, but he could not get any message to them. Yet he recalled that if he were to be touched by them, he could be relieved of his isolation immediately. He did not, however, recall the futility of his previous struggles; instead, he felt impelled to cry out for help, to get them to shake him, and to force his unresponsive body into activity. He was never able to call out or to move, and therefore he was never able to shorten any attack.

As the attack of sleep paralysis drew into its final moments, the generalized tingling sensation became more pronounced. He felt that his paralysis became deeper, perhaps as contrasted with the tingling. He knew that in the past the increased tingling sensation heralded the termination of his paralytic state. A final burst of effort resulted in the actual motion of his hand or his toe. The attack suddenly subsided. Instantly, he regained the control of his body.

The patient had learned long ago that after one attack had passed, if he were to lie in bed awaiting sleep he would probably go through another attack of sleep paralysis before morning. Through his past experiences, he knew that walking around the room would tend to prevent a second attack. He also believed that if he would fall asleep with his head propped up on pillows, he would suffer less attacks, "because his brain would have less blood."

With the relentless increase in the attacks of sleep paralysis, the patient became fearful and apprehensive of sleep itself. Nevertheless, even with the disruption of his night's rest, he was rarely tired on the following day.

A brief review of his background follows: His past medical history was normal except for the development of a gibbus in early childhood. The family history was suggestive of a possible sleep disorder in his brother and his mother. The patient was one of seven children, of whom five were females and two males. Two of his sisters had died at the age of 30, of complications resulting from childbirth. Of the surviving siblings, his brother had "frequent nightmares, which would cease as soon as his wife would shake him." The mother, now dead, used to have vivid "nightmares of being high up on a pinnacle." His father was able to relax and to sleep on any occasion, but he never felt any compulsion to sleep while he was at work.

The patient had no unusual personal habits. He did not drink alcoholic beverages or smoke tobacco. He drank one cup of coffee a day. He was college-educated and worked in a civil service capacity that provided him with an adequate income and security. His daily life at work and at home was one that was peaceful and satisfying to him.

On examination the patient appeared to be well developed and well nourished. He was 5 ft. (152 cm.) and weighed 118 lb. (53.5 kg.). His blood pressure was 120/70 mm. Hg. Physical examination showed a normal condition except for kyphoscoliosis of the thoracolumbar vertebrae. Results of laboratory examinations, including x-ray studies of the heart, lungs, and spine, red and white blood cell counts, serological tests for syphilis, urinalysis, and determination of the sedimentation rate, were normal. Prior to and during the current insulin therapy, the patient was examined by the consulting neurologist, psychiatrist, and psychologists. On the basis of psychiatric interviews, Rorschach tests, and Minnesota Multiphasic Personality Inventory tests, it was concluded that there was no evidence of a schizophrenic bodily preoccupation underlying this symptom of sleep paralysis. The tests indicated some evidence of hysterical tendencies, but not enough to support the diagnosis of a conversion symptom.

Insulin hypoglycemia therapy was begun on Oct. 8, 1951. Remission began immediately on the evening of the first injection and continued through the date of this report.

On Oct. 9, 1951, the patient stated that he had the most relaxed, uneventful evening of sleep since his disturbance began, 10 years before. It is reasonable to assume that this marked change in the quality of his sleep habits, which continued for the remainder of his treatment, reflected the onset of a remission. The smooth continuity of this remission was interrupted only once, on the night of Nov. 16, after a prolonged deep insulin reaction had been induced inadvertently on Nov. 14, and again on Nov. 16. The patient experienced a brief, but definite, sleep-paralysis attack, which lasted a few moments, and which he was able to break without difficulty by moving his hands. Treatment was stopped at once for one week and then resumed, with longer intervals between insulin administrations and with more care to keep the reactions to very mild sweating. This clinical result was a confirmation of a theoretical approach, which will be discussed later in this report.

Comment.—In the preceding 10 years the patient had suffered as many as 28 attacks a week. His longest spontaneous remission had occurred five years prior to treatment, for less than three weeks. All other spontaneous remissions were of less than one week and were rare. Since the beginning of insulin therapy the remission has continued for at least nine months,[2a] as of the time of writing, with the exception of the single recurrence on Nov. 16, after six weeks of continuous remission. In view of this record, the effectiveness of insulin in this case is impressive.

Interesting observations made during the current remission may throw light upon the mechanisms of recovery from sleep paralysis. On Jan. 14 and Feb. 12, 1952, after three months of insulin treatment, the patient exhibited two remarkable feats of spontaneous memory recollections of complicated word passages, with no possibility of suggestion on my part. One of these passages he had been unable to recite for the past 30 years, and the other for the past 20 years.

2a. As of Dec. 10, 1952, the remission in this patient had been present for 14 months. No treatment had been given since Oct. 10, 1952.

GENERAL COMMENT

The pathogenesis and pathology of sleep paralysis are unknown. However, in view of the prolonged and continuing remission in this case,[2b] it is probable that the disturbance is physiological and reversible. The area of the brain in which the physiologic disturbance is located is likewise unknown. Nevertheless, one is justified in suspecting that the hypothalamus is the probable center of this disorder. There is abundant evidence that the hypothalamus is closely connected with the regulation of sleep.[3] This function of the hypothalamus, whether it is conceived of in terms of a "sleep center" or of a "wakefulness center," is most likely involved in such sleep disturbances as narcolepsy. It is a reasonable hypothesis that the hypothalamus is similarly concerned with sleep paralysis. Such an assumption is especially justified, inasmuch as patients with narcolepsy have been benefited by insulin hypoglycemia administered in a similar manner.[4]

As a result of work in treating other conditions by means of mild insulin hypoglycemia stress reactions,[5] it occurred to me that more was being accomplished than the production of endogenous adrenocorticotropic hormone. The clinical observations hinged essentially upon the phenomenon of sleep characteristics of insulin hypoglycemia as compared with the effect of adrenocorticotropic hormone.

Hume produced experimental evidence indicating that insulin hypoglycemia acted directly upon the hypothalamus to produce a hormone that regulated the production of adrenocorticotropic hormone from the anterior lobe of the pituitary gland.[6] Whether Hume's explanation of the hormonal pathway is correct, or whether the adrenocorticotropic hormone is produced as a result of an intermediary action of epinephrine upon the anterior pituitary gland,[7] the action of adrenocorticotropic hormone upon sleep cannot be reconciled with the action of insulin hypoglycemia upon sleep. Administration of corticotropin characteristically results in insomnia, an action which is contrary to all observations on the effect of the insulin reaction for any condition.

2b. A second patient (R. B.) with sleep paralysis has also been treated by the same method as that described in this report. As of Dec. 1, 1952, uninterrupted remission of the sleep paralysis has been noted in the second patient for three months. Prior to treatment with insulin hypoglycemia the maximum time of spontaneous remission had been one week.

3. Hess, W. R.: Das Zwischenhirn: Syndrome, Lokalisationen, Funktionen, Basel, Benno Schwabe & Co., 1949. Rowe, S. N.: Localization of the Sleep Mechanism, Brain **58**:21-43 (March) 1935. Ranson, S. W.: Some Functions of the Hypothalamus, Harvey Lecture, Bull. New York Acad. Med. **13**:241-271 (May) 1937. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1 (Jan.), 145 (Feb.), 261 (March) 1929. Kleitman, N.: Sleep and Wakefulness, Chicago, University of Chicago Press, 1939.

4. Weitzner, H. A.: Insulin Hypoglycemia in Treatment of Narcolepsy, with Temporary Improvement, Permanente Found. M. Bull. **10**:153-156 (Aug.) 1952; Insulin Hypoglycemia and Narcolepsy, to be published.

5. Weitzner, H. A.: Role of Insulin-Induced Hypoglycemia in Treatment of Rheumatoid Arthritis and Certain Other Conditions, Permanente Found. M. Bull. **10**:112-118 (Aug.) 1952.

6. Hume, D. M.: Role of the Hypothalamus in the Pituitary-Adrenal Cortical Response to Stress, J. Clin. Invest. **28**:790 (July) 1949.

7. Long, C. N. H.: Factors Regulating Adrenal Cortical Secretion, in Symposium on Pituitary-Adrenal Function, read at the annual meeting of the American Association for Advancement of Science, New York 19, Dec. 28-29, 1951; Baltimore, Horn-Shafer Co., pp. 24-30.

In the treatment of rheumatoid arthritis and other conditions,[5] the use of insulin hypoglycemia usually produced a relaxed and uninterrupted night's sleep as one of its first results. This restoration of the normal pattern of sleep was not only for the immediate period of treatment but also for a prolonged period after insulin therapy had been discontinued. Observations such as these indicated that insulin hypoglycemia acted upon the hypothalamus not only to regulate the production of adrenocorticotropic hormone, but also to increase its power to regulate sleep.

The hypothalamus is one of the targets of insulin hypoglycemia. As a target, the hypothalamus is an exhaustible organ, eventually becoming refractory, or inhibited, a state perhaps corresponding to Selye's Stage 11 of resistance.[8] The refractory stage to further stimulation is easily reached, at least in rheumatoid arthritis.[9] In the present case the temporary inhibition on overstimulation was noted on Nov. 16, 1951. It was treated by less frequent insulin stress, with the result that the hypothalamus regained its sensitivity.

The mechanisms whereby insulin hypoglycemia restores the control of sleep to the hypothalamus, as well as to the efferent and afferent tracts that are involved, are not well understood. It is possible, however, that the phenomenon of memory restoration that was observed in this patient has some bearing upon the reactivity of the neurons concerned in the modification of sleep.

This patient demonstrated a restoration of unreinforced complicated memory reflexes due to his treatment with insulin hypoglycemia. Memory operates at a high level. The various theories of sleep are concerned with the relationship between the high levels of the cerebral cortex and the lower levels of the hypothalamus, between the conditioned reflexes that have learned the diurnal habits of sleep and the primitive center of the hypothalamus.[10] Thus, the phenomenon of the restoration of unreinforced reflexes which appeared during the continued remission of sleep paralysis suggests that the unreinforced conditioned-reflex aspects of sleep may be possible factors in the disturbance of sleep.

Restoration of unreinforced conditioned reflexes in animals were studied by Gellhorn and Minatoya with the use of insulin hypoglycemia.[11] These investigators found a good correlation between the restoration of unreinforced conditioned reflexes and the use of insulin hypoglycemia.

Although there is a similarity between the results of Gellhorn and Minatoya's investigation and my observations, more work must be done on the latter before any analogy can be drawn.

The appearance of the memory reflexes in no way lessens the fundamental importance of the hypothalamus in the control of sleep. The action of insulin hypoglycemia in sleep paralysis is most likely that of restoring this power to the hypo-

8. Selye, H.: Physiology and Pathology of Exposure to Stress, Montreal, Canada, Acta, Inc., 1950, p. 11.

9. Gordon, G. B., and Weitzner, H. A.: Rheumatoid Arthritis and Insulin Therapy, J. A. M. A. **145**:842 (March 17) 1951. Weitzner, H. A., and Snowden, V. L.: Insulin Hypoglycemia in Treatment of Rheumatoid Arthritis: Preliminary Report of 11 Patients, Permanente Found. M. Bull. **10**:119-128 (Aug.) 1952.

10. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, Baltimore, Williams and Wilkins Company, 1950, pp. 1052-1055.

11. Gellhorn, E., and Minatoya, H.: Effect of Insulin Hypoglycemia on Conditioned Reflexes, J. Neurophysiol. **6**:161-171 (May) 1943.

thalamic target. The pathways and influence of the hypothalamus upon the cortex by way of the thalamus have been demonstrated experimentally by many workers.[12]

Thus, even though hormonal activities are increased as a result of the application of insulin-hypoglycemia stress, there may also be a direct effect upon the hypothalamus by the action of insulin hypoglycemia. In the present case [2a] sleep paralysis was a clearly defined entity in which this hypothesis could be tested. The definite results in this case warrant a tentative affirmation of this hypothesis. More clinical and laboratory work is being conducted in a study of the possible factors involved. Inasmuch as the implications of this presented case have a direct bearing upon many functional disturbances, such as were brought out by Karnosh,[13] it is hoped that others may contribute studies along similar lines.

SUMMARY

In a patient with frequent attacks of sleep paralysis the disturbance was brought to a complete remission of at least nine months' duration.[2a] The remission began promptly after the first treatment.[2b]

The treatment consists of mild insulin-induced hypoglycemia of short duration, given at first every other day and then at gradually increasing intervals.

280 MacArthur Blvd., W.

Dr. J. P. Fitzgibbon, Chief of Neurological Service, who had studied the patient for the past five years, cooperated in referral of E. T. and in making available all his past records.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Hugh T. Carmichael, M.D., President, in the Chair
Regular Meeting, April 8, 1952

Tuberculomas of the Brain. Dr. Milton Tinsley and Dr. A. D. McCoy.

Since the advent of streptomycin, the treatment of intracranial tuberculoma has become considerably more hopeful. In a review of several series of cases of these lesions, the prognosis was found to depend upon the site of the lesion, on whether or not it was well circumscribed, and the postoperative medication. Lesions in the infratentorial group offered a graver prognosis, owing to the frequency of development of tuberculous meningitis. The treatment of choice resolved itself into a combination of surgery and intramuscular and intrathecal administration of streptomycin.

A series of four cases was presented, one of infratentorial and three of supratentorial tuberculoma. Two of the patients are still living, with only minor deficits, one having had a cerebellar tuberculoma and the other a cerebral tuberculoma. The third patient, who had a cerebral tuberculoma, died as the result of the development of tuberculous meningitis, and the cause of death of the fourth was purely surgical. The first three patients were given 0.5 gm. of streptomycin intramuscularly for six to eight weeks.

It was our impression that surgical treatment and intrathecal and intramuscular injection of streptomycin may be the treatment of choice for patients with tuberculoma and tuberculous meningitis, but that surgery and intramuscular use of streptomycin would suffice for patients who have only tuberculoma, but no meningitis.

DISCUSSION

Dr. Joseph Cascino: Several months ago I had the opportunity of operating on a patient with a tuberculoma who at last reports was doing well. One-half the tuberculoma was enucleated on one occasion and the other half about three weeks later.

Dr. Oscar Sugar: I have recently removed completely a tuberculoma of the cerebellum in a child, who has made apparently a complete recovery. I did not use streptomycin intrathecally, but gave it merely intramuscularly. I should like to point out in the presence of our distinguished visitor from France, Dr. Theophile Alajouanine, that before the advent of streptomycin the French neurosurgeons were able to remove a number of cerebellar tuberculomas with good survivals. I think we shall find that intrathecal use of streptomycin is not necessary in the treatment of intracranial tuberculomas.

Dr. Irving C. Sherman: In the first case the patient had focal seizures on one side. How could this be explained on the basis of a tuberculoma in the posterior fossa? Is it not likely that the patient had multiple lesions, or at least two lesions, the one in the cerebrum being silent at this time?

Dr. Milton Tinsley: The intraventricular use of streptomycin, as advocated by the French, was not effective in two cases I had. In both cases I inserted a catheter into the lateral ventricle for the instillation of streptomycin; both patients died of the tuberculous meningitis.

In answer to Dr. Sherman, a ventriculogram in the first case gave evidence of a filling defect in the right lateral ventricle. The patient did so well after the removal of the cerebellar tuberculoma that we did not feel anxious to make any further exploration.

Diagnosis and Treatment of Intracranial Aneurysms. Dr. Carl F. List, Grand Rapids, Mich.

A series of 73 verified cases of intracranial aneurysm of the carotid system was reported, including 8 cases of subclinoid aneurysm, 32 of supraclinoid aneurysm, 4 of bifurcation aneurysm,

6 of aneurysm of the middle cerebral artery, and 18 of aneurysm of the anterior cerebral artery (4 proximal, 13 of the anterior communicating artery, and 1 distal).

Accurate diagnosis must determine the size and location of the lesion, the presence (or absence) of bleeding, and the competency of the circle of Willis. Early and bilateral angiography is indispensable.

The aneurysm may be eliminated from the cerebral circulation by ligating its neck or by "trapping" (combined cervical-intracranial ligation). These procedures achieve permanent cure at a high risk. The alternative management, cervical ligation of the carotid artery, reduces the blood flow to, and the head of pressure in, the aneurysm; it carries a low mortality rate, but the observation time is insufficient to permit judgment of the long-term results.

Cervical ligation of the carotid artery was done in 29 cases, intracranial ligation in 25 cases, and combined cervical-intracranial ligation in 18 cases. The type and timing of the surgical procedure must be individualized. In aneurysm of the carotid system, cervical ligation is the safest effective treatment, to be followed by intracranial ligation only if symptoms persist or recur. Aneurysms of the circle of Willis or of vessels distal to it require intracranial ligation, provided surgical occlusion of vital vessels (middle cerebral or both anterior cerebral arteries) can be avoided. If this is impossible, cervical ligation or wrapping of the aneursym with muscle may be done.

The incidence of hemiplegia after ligation is high in bleeding aneurysm, but in most cases the hemiparesis will eventually recede. Hemorrhage and vasospasm in the neighborhood of the aneurysm favor healing but predispose to complications in treatment (hemiparesis).

DISCUSSION

DR. OSCAR SUGAR: Dr. List and I have been discussing aneurysms ever since we have known one another, which is about four years; as he has pointed out, one of the most important things is that one's results improve with experience. A recent symposium in Great Britain concerned with the treatment of acoustic neurinomas indicated that the older neurosurgeons do it so much better than the younger ones that the latter rarely get a chance to treat them. I am afraid that the same thing will be true of aneurysms. It is clear to me that the more aneurysms one treats, the better one gets at it. Perhaps it is because one learns on which to operate and which to leave alone. A recent visitor from the West Coast, who has done a number of arteriographic studies, stated the opinion that there are no contraindications to iodopyracet (diodrast®) arteriography. Most of us think that iodopyracet is a dangerous material to use in elderly patients. The treatment of such a patient who has bled inside his brain is exceedingly difficult. If there are definite third-nerve weakness and partial sensory loss over the forehead, the diagnosis of aneurysm is almost certain without an arteriogram, but the problem arises of what to do. Some of these patients get along well if left alone; some will die if left alone, and a number continue to have pain in the head if not treated. If the carotid artery is ligated and the patient survives, the relief of pain is most gratifying. Dr. Voris would say that such a procedure in a patient over 50 is very hazardous. As it is in the case of all aneurysms, the problem of the relatives is an acute one. If one does not operate on the aneurysm, one has to say to the relatives, and perhaps even to the patient, that a blood vessel has broken inside the head and it may break again at any time. On the other hand, if one operates on the patient, one must say that if all goes well and he wakes up from the operation, he may be hemiplegic or aphasic but that at least he will not die of bleeding from this aneurysm again. I certainly agree that cervical ligation is the safest way in which to treate an aneurysm, but it is not very pleasant to have the patient go home after such a procedure and die of the aneurysm bleeding again. I think it is worth while to take a chance on an intracranial operation after the aneurysm has bled; with aneurysms which only compress the third nerve, the cervical ligation, I think, is adequate. I have almost entirely given up clipping the neck of the aneurysm, and try to isolate it, clipping on either side whenever possible. I have given up the practice of isolating the carotid arteries before an intracranial attack. I admit that occasionally the aneurysm bleeds before one gets to it inside the head; even so, amputation of no more of the frontal lobe than is disconnected during a lobotomy allows rapid access to the aneurysm. For aneurysm of the anterior communicating region, I do an amputation before I look for the aneurysm in order to minimize the bleeding hazard. Actually, of course, one cannot predict even from a complete set of angiograms how large the aneurysm is or exactly where it is with

respect to important neighboring structures. I wish to commend Dr. List for his honesty in presenting the results of his now extensive experience to us: It will certainly give me, at least, heart in continuing.

DR. HAROLD C. VORIS: Our friend, Dr. Wallace Hamby, has said that when one attacks intracranial aneurysms surgically "he is hunting big game." Certainly, he is correct in the sense that these aneurysms can turn around and attack one while one is hunting them. Dr. List has proved himself not only a good hunter, but an honest one.

It is easy for me to compliment Dr. List on his presentation because I am in agreement with nearly everything that he has said. There is one exception. I am inclined to think that the patient with acute subarachnoid hemorrhage may have the tendency to further bleeding enhanced by immediate angiography. If such a patient is in relatively good condition and does not show evidence of further bleeding, I like to postpone angiography until his spinal fluid has cleared of blood. However, if evidence of further bleeding occurs, the angiographic procedure should be undertaken at once and surgical treatment instituted if possible. It is generally agreed that patients who show evidence of repeated bleeding have a very high immediate mortality.

I recently had an experience with a complication of surgical treatment that was new to me. A young woman with subarachnoid hemorrahge showed angiographic evidence of an aneurysm of the suprasellar portion of the right internal carotid artery. When the right internal carotid artery was occluded by percutaneous compression and the left carotid artery injected, there was inadequate filling of the right anterior and middle cerebral vessels. I concluded, therefore, that occlusion of the right internal carotid artery by cervical ligature or intracranial clip would be dangerous. It was decided to place a Selverstone clamp on the right internal carotid artery in the neck, so that the artery could be gradually occluded. This was carried out four or five days after the angiographic study. A modification of Sweet's apparatus was set up so that I could measure the pressure in the internal carotid artery above the clamp, as it was my intention initially to screw the clamp down until the pressure in the internal carotid artery was 50% of its initial value. As the needle in the internal carotid artery was being manipulated, a change in the patient's condition was noted. She was under intravenous thiopental sodium anesthesia, but when she recovered from the anesthesia I was not surprised to find she had a paralysis of her left upper extremity. The Selverstone clamp was immediately released, but was left in place. Fortunately, the paralysis rapidly cleared, and after two or three days I was able gradually, over a period of several days, to screw the clamp down and completely occlude the artery. Later the aneurysm was trapped by an intracranial clip proximal to the bifurcation of the right internal carotid artery, without complications.

In my opinion, when I manipulated the needle used to measure intracarotid pressure I dislodged a small mural thrombus which had formed after the earlier angiographic procedure. The needle had been introduced at or near the previous puncture of the artery. At the time of the sudden change in the patient's condition the Selverstone clamp had been placed about the artery, but had not been screwed down. When one is considering any manipulation of the cervical portion of the internal carotid artery during the first two weeks after operation, one must keep in mind the possibility of dislodging a mural thrombus.

DR. HERMAN CHOR: I should like to know whether or not the degree of hypertension has anything to do with the decision to use surgery in the treatment of the aneurysm, and whether it determines the type of procedure used.

DR. RASMUSSEN: Has Dr. List had any experience with methods of producing gradual occlusion of the internal carotid artery? How does he treat postligation hemiparesis?

DR. CARL F. LIST, Ann Arbor, Mich.: The Selverstone clamp was used in only one case. In order to reduce the blood flow gradually, I prefer to ligate the common carotid artery first and then, at a later stage, the external carotid artery.

When hemiplegia has developed after ligation of the carotid artery, stellate block has little to offer. I have used no specific measures in treatment of hemiplegia, but have employed only physical therapy for rehabilitation.

When an intracranial aneurysm is associated with arterial hypertension, the factor of risk is unquestionably higher and complications are apt to arise. I am not prepared to make a definitive statement regarding the effect of ligation of both anterior cerebral arteries. Two patients of the series presented died after ligation of both anterior cerebral arteries. In two

other observations the patients remained in a vegetative state. Falconer and Elvidge have reported cases with lasting mental disturbances similar to those following prefrontal lobotomy.

I agree with most of Dr. Sugar's comments. The decision to attack an aneurysm intracranially is often difficult to make after the patient has satisfactorily recovered from cervical ligation of the carotid artery. No matter how challenging the intracranial approach may seem to a daring surgical technician, a responsible physician will hesitate to gamble recklessly with the patient's life.

Disagreeing with Dr. Voris, I believe that the angiographic procedure may be carried out at any time, even during the phase of acute bleeding. There is no evidence that angiography may cause a new "blow out." On the other hand, ligation may have to be delayed because its risk is much higher during the phase of bleeding. This is particularly true in the case of the intracranial ligation. Craniotomy, therefore, should be postponed until the signs of subarachnoid hemorrhage have abated. The lower surgical mortality rate during the quiescent phase probably outweighs the potential risk of further hemorrhage during the period of waiting.

Non-Neoplastic Space-Occupying Lesions in Infants and Children. DR. JOSEPH CASCINO.

DISCUSSION

DR. HAROLD C. VORIS: I am sorry that Dr Cascino did not take more time to present his paper, especially that portion of it which deals with chronic subdural hematomas in infants and children. To me, that is a more interesting and profitable field than the cranial stenoses. My own experience with the cranial stenoses has been relatively slight. In the case of oxycephaly that Dr. Cascino described, the unsightly bulging of the subtemporal decompression fortunately did not develop. Although the patient was followed only a few months, the papilledema receded and her vision was saved. Perhaps I have been too conservative in dealing with microcephaly, but most of the patients I have seen appeared to have primary lack of cerebral development, with consequent premature closure of the sutures and failure of growth of the skull. Therefore I have operated in only a few such patients. However, when a child with cranial stenosis or microcephaly can be demonstrated to have premature closure of the sutures and there appears to be reasonable hope for normal cerebral development, surgical intervention is indicated.

DR. JOSEPH CASCINO: I should like to point out that Dr. Voris had taught me to place polyethylene film along the artificial sutures and that at the time of the second stage of the operation on this child I observed there were no adhesions between the bone and the dura. The material must be sterilized by placing it in a solution, and I would advise that in handling it large strips, rather than small ones, be cut. There were two reasons for difficulty in my operation: First, the material was cut too small, and second, I did not undermine the edges of the artificial sutures well enough to permit tucking of the polyethylene film.

PHILADELPHIA PSYCHIATRIC SOCIETY

Hugo Mella, M.D., President, in the Chair
Regular Meeting, March 14, 1952

Psychiatry in the Far East: Psychiatry with a Division. DR. WILLIAM HAUSMAN, Dayton, Ohio.

This discussion of Division psychiatry was directed toward the comparison of elements of this practice with civilian psychiatry. The psychiatrist brings to the Division his personal security and initiative, his professional training and experience, which are important in any therapy, together with military training and combat-area orientation. He finds it important to identify with the combat unit, rather than with the individual soldier. He must deal also with rapidly changing military tactics, varying staff and medical cooperation, and needs for maintaining flexible arrangements for medical mobility and evacuation. Most of these problems are unique to combat psychiatry. Added to these are his own anxieties related to his proximity to a rapidly changing front.

Basically, his patients deal with the always-present anxieties according to previous behavior patterns, as do any psychiatric patients. While the soldiers face unusually grave dangers, their

ego defenses are greatly bolstered by the potent integrating force of membership in a fighting unit and by other morale elements, at an intensity that seems unique to the combat situation. The Division psychiatrist attempts to mobilize these forces in a rapid, but most dynamic, type of therapy situation, to maintain fighting strength, and to avert the crippling sequelae of secondary gain.

Far-Eastern Psychiatry in a Naval Hospital in Japan During the Korean War. Dr. Ralph B. Little.

The author presented briefly his experience as a naval psychiatrist assigned to the Navy's only commissioned hospital in Japan in the winter of 1950-1951, during active Korean hostilities. All types of psychiatric disabilities were encountered, for, in addition to the Marines from Korea, many naval personnel members of the Far-Eastern command were seen. Difficulties in treatment were often determined by the problem of secondary gain and poor motivation. Psychotherapy, which had to be short, consisted mostly of presenting a superficial understanding of the problem, an attempt at relief of guilt, and respect for the individual. Other methods of treatment, which were used with poor success, included insulin subcoma therapy, group psychotherapy, and amobarbital (amytal®) sodium abreaction. Because Marine patients were seen usually three or four days after combat, symptoms had been fixed. It was difficult to speculate on the implications of future problems these men may present, for it was felt that many would improve when evacuated to the United States, with the possible attainment of secondary gain; others would need additional management and treatment.

Implications of the Practice of Psychiatry in a Hospital in the Korean War. Dr. Harold Kolansky.

The author related his experience as chief of a psychiatric service in an Army hospital in Korea. The therapeutic focus was rapid, forward aid to the patient whose adaptive responses had been temporarily reduced in efficiency, with the idea that such treatment would prevent progression of neurotic symptoms and the need for treatment in the United States. As a result, 70% of the patients were returned to duty in Korea. Among factors operative in the somewhat higher return to duty than was seen during World War II were (1) rapid evacuation by air, (2) minimization of secondary gains through adherence to the focus mentioned above, (3) short hospital stay (average two to four days), and (4) the conveying of the conviction of therapists that early return to duty was therapeutic (lessening guilt over separation from the group).

The use of the term "combat exhaustion" and its advantages was discussed.

Types of cases seen were discussed, with illustrative histories, and the importance the following factors in the psychogenesis of the breakdown were stressed: (1) prolonged exposure to situations in which counterhostility could not be expressed; (2) repeated exposure to death and mutilation of close friends; (3) sense of guilt over expression of hostility, and (4) breakdown in group morale.

Observations of a Civilian Psychiatrist. Dr. William Peltz.

Trips by civilian consultants in most of the specialties have been made to the European Theater of Operations and to the Far-East Command during the past several years. Dr. Peltz made the fifth such trip by a civilian psychiatrist. He outlined the purpose of these trips, as well as a brief itinerary. A résumé of the similarities and the differences between psychiatry in the Army in World War II and psychiatry in the Korean campaign was presented, and the chief types of treatment employed, from that at division level to that in the base hospitals and the convalescent hospitals in Japan, were discussed. A firm, realistic, suppressive type of therapy is used at the forward echelons, and the more expressive type of psychotherapy, in the rear echelons. Electroshock therapy and substupor insulin therapy are used in the base hospitals, and occasionally narcosynthesis is utilized at various levels. Group therapy and hypnosis are not employed. Eight or more research projects which have been going on in the area, various contributions to the literature, and medical and psychiatric meetings or symposia in the area were mentioned. Finally, the excellence of morale among the troops was noted.

DISCUSSION ON PREVIOUS PAPERS

DR. CALVIN DRAYER: I should like to comment on the contrast between the present situation and that during the recent war. Ten years ago there was a dearth of psychiatric planning. The lessons presented tonight were well learned in World War I. They appeared in print in 1929, when the "Medical History of the First World War" was published. In the 10 or 12 years following the publication of that history, this knowledge was not used by the Americans. The British used it more than the Americans, and at the beginning of the second war, or in 1940, we had completely forgotten these lessons.

In the Korean campaign it took three months to set up an effective component. This was demonstrated on two or three occasions, rather conclusively in each case. Here is a demonstration of psychiatry in action. It may not sustain itself in time of peace without a great deal of interest on the part of groups such as our own. It seems to me important to bring the subject up recurrently, review its status, and see that officers in all the forces are thoroughly supported in what they try to do in times of peace.

Two or three specific points deserve comment. Narcosynthesis has not been used in the Korean campaign as in World War II. It had its place but did not get many men back to duty. Dr. Peltz had a great deal of experience with hypnosis in a combat area. In the area where I was active, we were working toward the technique described, the face-to-face interview.

The matter of assignment was mentioned briefly by one of the speakers. There is a three-month limitation; that is, a man must be reevaluated within three months. This creates problems, but also has advantages. It prevents the build-up of the limited disability classification.

I should like to hear the reaction of some of the speakers to two or three questions. Does the psychiatric program meet the needs of the combat area? Are there any considerable number of psychiatric disabilities which escape treatment under the guise of psychosomatic disease? What is the status of the man returned to duty, and what is the effect on the man after he returns to duty? That is, are we paying too high a price for sending him back?

DR. M. M. PEARSON: I should like to ask one question regarding prognosis. Dr. Kolansky did not think that the psychiatric casualties who were reevaluated and sent back to duty would break down again. He believed that the outlook was rather good. I should like to hear what the other two consultants think. The authors give an interesting picture of combat psychiatry. There is one thing lacking in this meeting; we should have had a psychiatrist who saw casualties after they came back—those who were not psychiatric casualties until after their return to the States.

DR. WILLIAM HAUSMAN, Dayton, Ohio: I think I can answer some of these questions, because I was close to the men. We were wrong at times. The example I gave of the man we sent back to duty after an attack of depression was one. We had some good controls. The sergeants and their men did not like it when we sent back some of the men. We were told not to send them back. At first I felt badly about sending them back. Later I was surprised by the rather small number of men we sent back who returned to us. Some would come back almost at once. After this they would often make a satisfactory adjustment. I remember one episode I saw enacted: A man was crying and carrying on in his aid station, and the medical officer slapped him and said, "Go on back where you were." Five or six months later the man came to the same officer on duty in the first-aid station and said, "Remember when you slapped me and sent me back to duty? Well, I did go back, and I did my job." The positive effect of this on the group seems to be tremendous.

I felt that one could handle the problems provided one had the cooperation of the line officers. One of the regimental commanders whose statistics had been the highest was disturbed about the situation; he sent the men back and then ordered that there should be no psychiatric casualties. However, that sort of thing was the exception, rather than the rule.

DR. HAROLD KOLANSKY: We had several impressions as to what would happen to these men when they were sent back to duty. A group with conversion hysteria, sent back with paralysis of a limb, were disposed of with amobarbital, and they would come back with paralysis of another limb or some other symptom.

As to the men who were sent back to the United States with relatively few symptoms, psychiatrists had the impression that they were men who had once been through hospital

evacuation. I have seen several men on ships whom I had sent back, and they thanked me for returning them to duty so that they could sweat it out and go home through channels of regular rotation.

Another problem is that of personality disorders, e. g., drug addiction. Such men, after they were sent to us and returned to duty, would bounce back. They were very bad for the morale.

DR. WILLIAM PELTZ: In answer to Dr. Drayer's questions: Does the program meet the need of the combat area? I think it does.

There are numerous things that came up. The great need until recently was a psychiatrist for the Eighth Army, which includes all the Americans and the British. In the last two months a psychiatrist has been provided for the Eighth Army, and this is having good results.

What is the effect on the others of returning these men? If psychiatric casualties were not returned to duty, the effect would be to point an easy way out.

In the German army in World War II there was a very low incidence of psychiatric disability. When a man broke there, he was sent to the work camps, and his fate was worse there than in a combat outfit. When a man is returned to duty, it gives the men the idea, "These psychiatrists are pretty tough fellows," and the secondary gain has been reduced. There were some we sent back who were pretty difficult to deal with, and who were disturbing to morale; yet if they had been discharged, it would look like an easy way out.

DR. CALVIN DRAYER: We feel that the program presented tonight is not a pale facsimile of the German attitude. The German statistics are extremely misleading. They do not deal as constructively with reactions as this program does. The German attitude is extremely punitive. While we may be firm, we would not drag a man out to return him to duty. It is a constructive experience for the person who does make use of group loyalty.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

AMOUNTS OF GLYCERYLPHOSPHORYLCHOLINE IN SOME MAMMALIAN TISSUES. G. SCHMIDT, L. HECHT, P. FALLOT, L. GREENBAUM and S. J. THANNHAUSER, J. Biol. Chem. **197**:601, 1952.

A chemical method for the quantitative determination of *l*-α-glycerylphosphorylcholine and of the preformed choline fraction in tissues is presented. Amounts corresponding to at least 1 mg. of choline in the final aliquots are required. The amounts of glycerylphosphorylcholine and of the preformed choline fraction in some organs were determined. Large concentrations of glycerylphosphorylcholine amounting to more than one-half the phospholipide choline were found in fresh lamb liver, but only negligible amounts of water-soluble choline compounds were found in fresh livers of weanling or adult rats. The rapid enzymatic degradation of phospholipides in suspensions of rat intestines was accompanied by the corresponding increase of the water-soluble choline compounds. After incubation at pH 8 the optimum of phosphodiesterase activity, most of the water-soluble choline fraction consisted of free choline; after incubation at pH 5.2 most of this fraction consisted of glycerylphosphorylcholine. The observations presented suggest the general importance of glycerylphosphorylcholine as an intermediary in the phospholipide metabolism of mammalians, regardless of its different concentrations in the fresh livers of different species.

PAGE, Cleveland.

ACTION CURRENTS IN SINGLE AFFERENT NERVE FIBERS ELICITED BY STIMULATION OF THE SKIN OF THE TOAD AND THE CAT. J. MARUHASHI, K. MIZUGUCHI and I. TASAKI, J. Physiol. **117**:129, 1952.

The authors recorded action potentials in isolated single afferent nerve fibers from the skin of toads and cats. Impulses were induced by applying various types of stimuli (heat, cold, light touch, pressure, needle prick, etc.) to the skin. Fibers from the toad skin were classified as tactile fibers, pressure fibers, large and small nociceptive fibers, and unmyelinated fibers. From the cat's skin, tactile fibers, pressure fibers, large and small nociceptive fibers, cold fibers, wide-receptive fibers, fibers associated with hairs, fibers arising in subcutaneous tissue, scratch fibers, and unmyelinated sensory fibers were recognized. The different classes of fibers were characterized by differences in fiber diameter and conduction velocity and in the the size and shape of the receptive area in the skin; there were also differences in amplitude of the nerve impulses and in the rate of adaptation of the endings. The wide-receptive fibers are of interest because of the very large skin area (from 3 by 5 to 5 by 9 cm.) supplied by a single fiber and because they apparently enter the spinal cord via the ventral roots. They respond to extremely light touch or to pressure on the hairs in the skin area supplied.

THOMAS, Philadelphia.

ANALYSIS OF AFFERENT AND EFFERENT SYSTEMS IN THE MUSCLE NERVE OF THE TOAD AND CAT. Y. KOBAYASHI, K. OSHIMA, and I. TASAKI, J. Physiol. **117**:152, 1952.

By the method of recording action currents from individual nerve fibers, an attempt was made to survey the functions of all the nerve fibers contained in the muscle nerves of the toad and the cat. Afferent nerve fibers arising in the toad muscle were classified into four groups: (*a*) The tonic afferent fibers arise in the belly of the muscle, where the muscle spindles are located; they are 8 to 12 μ in diameter and have been investigated extensively by previous workers. (*b*) The phasic afferent fibers are 7 to 11 μ in diameter and arise in the perimysium. (*c*) The small myelinated afferent fibers are 2.5 to 5 μ in diameter; some respond to intense stretching or to injurious pinpricks with only a few impulses. (*d*) Unmyelinated fibers apparently transmit

slow afferent impulses. In the muscle nerve of the cat there are also tonic, phasic, and small myelinated afferent fibers, similar to those found in the toad's muscle nerve. The small myelinated afferent fibers seem to reach the spinal cord, at least partly, by way of the ventral spinal roots. Large and small tendon afferent fibers were isolated from a "non-motor" bundle entering the extensor digitorum muscle. The toad's muscle nerve contains a large number of unmyelinated efferent fibers which transmit slow impulses from the sympathetic chain to the muscle. Similar slow efferent impulses were recorded from the rabbit and the cat muscle nerves. It was concluded that the tonus and the decerebrate rigidity in the cat muscle are maintained mainly by the activity of the small myelinated efferent nerve fibers. Both large and small efferent fibers take part in the spinal reflexes. In all cases, impulse discharges in small efferent nerve fibers are provoked more readily than discharges in large motor fibers, and the frequency of discharge is higher in the small fibers than in the large ones.

Abstractors Note: Kuffler and associates (*J. Physiol.* **113**:283, 1951) have shown that the small myelinated efferent fibers go not to muscle fibers but to muscle spindles, and that their effect is to increase the responsiveness of these stretch receptors.

THOMAS, Philadelphia.

SENSORY RETURN IN PARTIAL AND RECOVERY SPINAL CORD LESIONS. B. BOSHES, M. BROWN, and R. L. CROUCH, Neurology **2**:81 (March-April) 1952.

For this study of sensory recovery in traumatic lesions of the spinal cord only cervical and fairly high thoracic lesions were selected. Of 378 patients who were observed originally, 93, or 24.8%, had lesions which were subsequently found to be incomplete. Of these, 89, or 25.6%, had some kind of sensory return.

The pattern of return was quite variable. Most frequently there was a recession of the anesthesia and paralysis in a segmental manner. At other times function returned first in the sacral regions and then ascended. In others there was a gradual return of function over the whole affected area at the same time. Somewhat of a variation of this method was a patchy return over the affected area.

There was a high percentage of correlation of sensory modalities carried in the same fasciculi, indicating that the return of sensory functions was on an anatomic, rather than a functional, basis.

The time after injury for return of function was usually within three months. There were some exceptions to this. Although good recovery was generally associated with early recovery, the authors found that this was not invariably true.

ALPERS, Philadelphia.

BEHAVIOR DEFICITS FOLLOWING DIENCEPHALIC LESIONS. J. S. MEYER and J. HUNTER, Neurology **2**:112 (March-April) 1952.

The aim of this series of experiments was to make well-localized lesions in anatomic components of the diencephalon in order to observe behavioral and electroencephalographic changes following such lesions, in the hope of clarifying some of the neural mechanisms related to sleep and the unresponsive states. Twenty-three cats and two monkeys were used.

These experimental studies revealed that akinetic and apathetic states may be obtained with lesions in the region of the anteromedial portion of the thalamus and the upper end of the mamillothalamic tract, and that these states are associated with electroencephalographic abnormality showing similarities to records obtained during sleep. Sensory stimulation, however, never produces the same degree of cortical excitation in these experimental animals as in the normal animal.

Akinetic and cataleptic states were produced in cats with lesions in the region of the midportion of the mamillothalamic tract, and symptoms of catalepsy and unresponsiveness were obtained with both unilateral and bilateral lesions in the region of the mamillary bodies and the inferior portion of the mamillothalamic tract. Spontaneous electroencephalographic changes were not prominent in this group.

Meyer and Hunter conclude that the effects produced by localized coagulation of the diencephalon in cats suggest that regions in the vicinity of the mamillothalamic tract and adjacent structures play an important part in the mechanism of responsiveness in animals.

ALPERS, Philadelphia.

ACTION OF ADRENALINE [EPINEPHRINE] AND NORADRENALINE [ARTERENOL] ON THE TREMOR IN PARKINSON'S DISEASE. H. BARCROFT, E. PETERSON, and R. S. SCHWAB, Neurology **2**:154 (March-April) 1952.

The effect of intravenous injection of epinephrine and arterenol on the tremor of Parkinson's disease was investigated in 15 patients. The action of the following drugs was investigated: (1) The action of epinephrine in patients after withdrawal of medication, (2) the action of arterenol in patients after withdrawal of medication, and (3) the action of epinephrine in patients while receiving medication. The drugs used for medication were diphenhydramine (benadryl®), caramiphen hydrochloride (panparnit®), and trihexyphenidyl (artane®).

Barcroft and his co-workers found that in more than half the patients epinephrine caused a marked increase in the tremor. In no patient did arterenol have any significant effect. The effect of epinephrine on the tremor was much reduced when the patients were being treated with the so-called antispasmodic drugs.

The effect of epinephrine on the tremor was not due to the rise in arterial blood pressure, nor was it due solely to apprehension. Some other action is involved, probably within the central nervous system.

The authors point out that the reason that epinephrine enhances the tremors and arterenol does not is unknown. The reason that the antispasmodic drugs used in the treatment of the disease reduce the effect of epinephrine on the tremors is also unknown.

ALPERS, Philadelphia.

EFFERENT CONNEXIONS OF THE HUMAN PREFRONTAL REGION WITH REFERENCE TO FRONTO-HYPOTHALAMIC PATHWAYS. E. BECK, A. MEYER, and J. LEBEAU, J. Neurol., Neurosurg. & Psychiat. **14**:295 (Nov.) 1951.

Efferent connections of the frontal pole were studied by the Glees silver-impregnation method in a case of topectomy of Area 10/FE. The findings were contrasted with those in a case of rostral leucotomy, aimed at undercutting Areas 9/FDm and 10/FE.

It was found that efferent fiber systems arising from the extensive frontal poles are few. They are confined to a distinct projection upon the dorsomedial thalamic nucleus, some short association fibers to the adjacent prefrontal cortex, a few callosal fibers, and a weak contribution to the superior longitudinal fasciculus. There is no connection with the hypothalamus or any other subcortical centers.

A direct corticohypothalamic pathway was demonstrated originating anterior to the agranular frontal cortex and terminating in the ventromedial and lateral hypothalamic nuclei. Whether this tract arises from the medial orbital or dorsal frontal cortex could not be determined from this material.

ALPERS, Philadelphia.

Diseases of the Brain

SACROCOCCYGEAL CHORDOMA. T. J. SNODGRASS and H. M. SUCKLE, A. M. A. Arch. Surg. **65**:181, 1952.

Sacrococcygeal chordoma is a rare, slow-growing, invasive, but rarely metastasizing neoplasm of the bone that arises from remnants of the notochord.

After a brief review of the literature of 143 cases, the authors describe the case of a woman aged 70 with sacrococcygeal pain and a large presacral mass. Roentgenograms revealed a destructive lesion in the sacrum and coccyx, as well as a presacral soft tissue mass containing calcium deposits. The tentative diagnosis of chordoma was confirmed by biopsy, and at a later stage the entire tumor, weighing 250 gm., was removed. Thirteen months after operation the patient was doing fairly well, but examination revealed questionable evidence of recurrence.

Biopsy verification is always desirable before radical surgery is attempted. Incomplete removal of chordoma is always followed by recurrence. Adequate resection of the invaded sacrum is necessary; the colon must be freed from the tumor, and the nerve supply for bladder and rectum should be carefully preserved. X-ray therapy is apparently of little value.

LIST, Grand Rapids, Mich.

ELECTROENCEPHALOGRAPHY OF THE NEWBORN. J. G. HUGHES, F. S. HILL, C. R. GREEN, and B. C. DAVIS, Am. J. Dis. Child. **79**:996 (June) 1950.

Electroencephalography was employed to determine the effects on cortical activity of the newborn infant of various analgesic drugs given to the mother during labor. Groups of mothers were given meperidine, vinbarbital, or morphine; some received scopolamine. The central purpose of the work was to evaluate doses of the drugs which would give adequate relief to the mother but which would not unduly depress the brain of the baby. Only babies born of mothers whose labor and delivery were considered to be completely normal were included in the study.

The data show that the higher the dose of any of the analgesic drugs administered, the greater the incidence of delay in primary respiration of the newborn. Clinical drowsiness of infants on the first day of life correlated fairly well with the size of the dose of the analgesic agent.

With all the analgesic drugs studied and with the various doses used, the majority of newborn infants showed cortical suppression. While the chief electroencephalographic finding was a decrease in amplitude of brain potentials, many of the tracings also showed bursts of slow waves of high microvoltage. In addition, in the morphine series, a few of the tracings showed fast activity, ranging in amplitude from 10 to 40 μv and in frequency from 15 to 20 cps.

Of special interest was the effect on the babies born of mothers given more than 8 grains (0.52 gm.) of vinbarbital sodium, particularly when an intravenous injection of the drug was administered shortly before delivery. The authors believe that doses in excess of 8 grains (0.52 gm.) are definitely dangerous and that intravenous injection given within a few minutes prior to delivery carries a great hazard to the infant.

ALPERS, Philadelphia.

CORRELATION OF EPILEPTIC SEIZURES, ELECTROENCEPHALOGRAMS, AND EMOTIONAL STATE: SOME PRELIMINARY OBSERVATIONS IN SEVERAL CHILDREN. I. N. BERLIN and C. L. YAGER, A. M. A. Am. J. Dis. Child. **81**:664 (May) 1951.

Four brief case histories present observations on the effect of the feelings of the child's parents on the child's emotional state, and thus on the frequency and severity of epileptic seizures, as well as on the abnormality of the electroencephalograms.

From their preliminary observations the authors are of the opinion that a direct correlation may exist. They state that psychotherapy with both child and parents may prove to be an important factor in the treatment of epilepsy in the child in whom psychologic conflicts exist in addition to the epilepsy.

ALPERS, Philadelphia.

MULTIPLE SCLEROSIS: A CORRELATION OF ITS INCIDENCE WITH DIETARY FAT. R. L. SWANK, Am. J. M. Sc. **220**:421 (Oct.) 1950.

Swank reconsiders the evidence that there is a geographic variation in the incidence of multiple sclerosis and presents evidence that variations in dietary fat are more significantly correlated with the development of multiple sclerosis than are climatic conditions. In Norway between 1935 and 1939 there was an increasing consumption of margarine, and with this an increasing number of cases of multiple sclerosis. During the German occupation there was a 65% decrease in consumption of fat, with apparently an adequate caloric intake. In this period the incidence of multiple sclerosis was low, but two years after the war the number of cases had increased 2½ times. In Denmark there was also a low incidence of the disease during the period of economic depression. During the German occupation, the incidence of multiple sclerosis was low in the cities, but in the rural areas, where the populace apparently consumed the fat products to avoid export, the incidence of the disease increased. Similar observations were made in the Netherlands. It was also observed that when Jewish refugees reached Switzerland and their diet improved, there suddenly developed a large number of cases of multiple sclerosis. Among the Swiss themselves, the highest incidence was found among the Germans, who had the highest dietary fat consumption.

BERLIN, Chicago.

PULMONARY EDEMA IN PATIENTS DYING WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM. R. PAINE, J. R. SMITH, and F. A. HOWARD, J. A. M. A. **149**:643 (June 14) 1952.

A brief survey of the literature indicates that pulmonary edema may be an important complication of significant neurological disease. Most reported attempts at treatment have been governed by the neurogenic concept of pulmonary edema formation; however, it is well known that acute pulmonary edema is a common result of acute myocardial failure. The authors raise the question whether patients exhibiting neurological disease and pulmonary edema may also have significant cardiovascular failure as a sequel to the major illness, even though clinical evidence of cardiovascular damage is not present.

Study was made of necropsy protocols of 81 consecutive patients who died with major disease of the central nervous system. Special attention was given to the presence of pulmonary edema and morphological evidence of cardiovascular disease. In a parallel series, the records of 57 patients who died of various conditions exclusive of neurological disease were likewise chosen in consecutive order, and the notations on the lungs and circulatory apparatus at autopsy were examined.

Paine and his co-workers found that comparison of the two groups of patients showed that the incidence of congestion and edema of the lungs was no greater in persons who died of neurological disease than in those having no evidence of nervous disorder. Organic cardiovascular disease was present in the majority of patients with pulmonary edema irrespective of the presence of central neural illness. These observations do not suggest an important or unique neurogenic role in the occurrence of pulmonary edema.

The evidence here reviewed suggests that the occasional occurrence of acute pulmonary edema in the presence of an apparently normal heart may be due to heart failure produced by the extreme stress of neurogenic hypertension, cardiac and respiratory arrhythmias, and hypoxia.

ALPERS, Philadelphia.

THE ELECTROENCEPHALOGRAM AFTER HEAD INJURY. I. C. KAUFMAN and A. E. WALKER, J. Nerv. & Ment. Dis. **109**:383 (May) 1949.

Kaufman and Walker studied 241 patients with post-traumatic epilepsy and 83 patients with penetrating head injury who did not have epileptic seizures. For 91.3% of the epileptic and for 77.1% of the nonepileptic patients the tracings showed abnormalities, with a focal abnormality for 83.8 and 67.5%, respectively. In both groups there was approximately a 22% incidence of paroxysmal abnormality. In 62.6% of the epileptic patients seizures developed within six months of injury, and in 92%, within one year. Of the 29 epileptic patients with bilateral injury, 11 had only unilateral abnormalities.

Since only 22% of the epileptic patients had clearly localized electroencephalographic abnormalities, metrazol® (pentylenetetrazole) was used to activate the focus selectively, resulting in a localized alteration in 67.9%. It was found that activation does not give consistent results in the same patient, so that repeated examinations are statistically worth while.

In 39 patients exploration was carried out because of uncontrollable epilepsy. In all patients in whom a focus was revealed by activated electroencephalography, operation confirmed the locus. Of 34 cases, 41% had preoperative paroxysmal abnormalities; three months later only 14.7% had this feature. Metrazol® activation gave results in 13.7% before operation, but three months after operation 51.7% showed no response.

The authors state that from the electroencephalogram alone one cannot tell or foretell whether a patient with a severe head injury has or will have epilepsy. Activated electroencephalography appears to be a useful diagnostic aid in determining the type of seizure, the location of the focus, and possibly the prognosis, in cases of post-traumatic epilepsy.

FARMER, Philadelphia.

FAMILIAL HAEMANGIOMATA OF THE CEREBELLUM. H. O. TONNING, R. F. WARREN, and H. J. BARRIE, J. Neurosurg. **9**:124 (March) 1952.

Hemangioblastomata of the central nervous system are isolated lesions unless they constitute part of the hereditary disease known as the von Hippel-Lindau syndrome, when they may be associated with angiomata of the retina and spinal cord, multiple cysts of the kidneys and pancreas, and even renal carcinoma.

The authors stress the importance of taking a careful family history when vascular tumors are discovered in the brain. Three cases of the Lindau-von Hippel syndrome among siblings in a family of four children are reported.

One patient died after removal of a cerebellar tumor and was found to have cysts in the lung, kidney, and pancreas. One died of renal carcinoma after successful removal of a cerebellar angioma. One has had a successful removal of a cerebellar angioma.

The authors believe that the condition must be due to a hereditary, but persistent, abnormality in which there is a lack of integration between blood vessels and their field of supply. In the phase of fetal development this leads to cysts, and in later life to neoplasms.

ALPERS, Philadelphia.

CHORDOMA: EXPERIENCE WITH THIRTEEN CASES. J. L. POPPEN and A. B. KING, J. Neurosurg. **9**:139 (March) 1952.

Chordomas producing clinical symptoms are rare. Poppen and King report 13 cases, the lesion being intracranial in 7 and arising in the spine in 6.

Neither the clinical history nor the examination revealed anything that was thought to be characteristic of a chordoma. The x-ray examination was most helpful in revealing the position and extent of the lesion but was of little help in determining the cause. The bony involvement, of which destruction was the most important element, nearly always suggested metastatic carcinoma. In several instances sclerosis and new-bone formation were noted.

Wherever chordomas are situated, they look more or less alike. They appear as lobulated, gelatinous masses, often with a thin capsule. When incised, the tissue is soft, yellowish or raspberry, and jelly-like, and can sometimes be aspirated with a large suction tube. Occasionally a chordoma may be a firm, red, cartilaginous mass.

Penetration of the dura may lead to the correct diagnosis. This is an uncommon occurrence with any type of tumor except the chordoma. Few chordomas metastasize. They show great histologic variations, considerable variation being found even within a single tumor.

Although it has repeatedly been stated that most patients do not live much longer than eight months after they are first seen, and this was generally true in the present series, symptoms are often present for years before the patient seeks treatment. Some patients have been known to live a decade, and two of the patients in this series were still alive at the time of the report, more than six years after the tumor was verified.

The authors are in agreement with the statement that the tumor can rarely be completely removed surgically. This was possible in only one of their intracranial cases and in none of the spinal cases. Although surgical treatment leaves much to be desired, an occasional patient may be benefited greatly by it, so that surgical intervention should not be withheld.

Despite the fact that chordoma is an embryonal tumor, it is highly resistant to x-rays. These workers believe x-ray therapy should be used, but that the doses must be very large to be of value.

ALPERS, Philadelphia.

APOPLEXY IN A PITUITARY CHROMOPHOBE ADENOMA, PRODUCING THE SYNDROME OF MIDDLE CEREBRAL ARTERY THROMBOSIS: CASE REPORT. M. T. SCHNITKER and H. B. LEHNERT, J. Neurosurg. **9**:210 (March) 1952.

The syndrome of pituitary apoplexy due to degenerative changes in adenomas of the pituitary body is a relatively rare condition, usually manifested by sudden onset of oculomotor nerve paralyses, coma, and bloody cerebrospinal fluid. The clinical diagnosis is difficult, and treatment, both expectant and surgical, is unsatisfactory.

The present case is reported because the clinical manifestation of the pituitary apoplexy was quite unlike the picture as presented in the literature. The symptoms of coma, diplopia, and ophthalmoplegia are given as the usual clinical picture in pituitary apoplexy. The authors' patient presented transient coma, left hemiplegia, and no ocular symptoms whatever. Hence in this patient, aged 65, with sudden coma and left hemiplegia with clear cerebrospinal fluid, attention was directed toward treatment of thrombosis of the right middle cerebral artery, rather than of pituitary apoplexy in the absence of pituitary neighborhood signs, even though it was known that the patient harbored an old chromophobe adenoma (operated on 11 years previously).

A right stellate ganglion block was carried out 18 hours after the initial catastrophe, with 20 cc. of 1% procaine hydrochloride. A good Horner syndrome was produced on the right side, and within five minutes he was able to lift his left arm and leg off the bed. On the following morning he still had some movement of the left side. Another right stellate ganglion block was done, but without improvement. Two days later the patient became more drowsy, and the left hemiplegia returned. There was no change in ocular signs or other cranial nerves. He became irrational, progressed into deepening coma, and died 15 days after admission to the hospital.

Autopsy revealed (1) pituitary adenoma, chromophobe, sinusoidal type, with recent hemorrhage into the tumor; (2) compression of the right middle cerebral artery by the hemorrhage into the pituitary tumor; (3) extensive infarct, with encephalomalacia in the right cerebral hemisphere; (4) status postcraniotomy (old), with atrophy of the right frontal lobe and dural adhesions to the brain, and (5) rheumatic heart disease, chronic. ALPERS, Philadelphia.

DISABILITY CAUSED BY BRAIN WOUNDS: A REVIEW OF 1,166 CASES. W. R. RUSSELL, J. Neurol., Neurosurg. & Psychiat. **14**:35 (Feb.) 1951.

This paper is based on a follow-up study which has continued throughout and since World War II. Its main purposes are concerned with the problems regarding the effect of lesions of different areas of the brain, as well as with the problems of rehabilitation presented.

In the late war most patients with head wounds who reached the hospital alive were found to have been struck by small fragments of high-explosive shells. These metal fragments, on striking the head, lodged in the skull, glanced away, or cut into the brain. In any case a small shower of bone fragments was often projected into the brain from the point of impact. Many of the resulting lesions are remarkably self-limited and provide unique material for the study of focal brain lesions. Wounds to all parts of the parietal, temporal, and occipital lobes are very likely to cause focal symptoms, temporary or permanent, such as paralysis, aphasia, or partial blindness. The very high incidence of early focal signs in brain wounds seems to depend partly on the spread of a shock effect from the site of the wound. A large number of patients with early signs recover well. However, the incidence of permanent major physical disability is over 30%.

In 306 of a series of 631 cases the injury was followed by post-traumatic epilepsy. The incidence of post-traumatic epilepsy is higher when the wound occurs in some regions (e. g., the parietal lobe) than in others. Although the incidence of post-traumatic epilepsy is so high, the seizures in most cases are so infrequent and so easily controlled by anticonvulsant drugs that post-traumatic epilepsy is seldom a very serious disability, a point of great importance in assessing the need for surgical treatment.

Contrary to Penfield's thesis that progressive gliosis in relation to the brain scar is the main factor in producing fits, and to the view that a constitutional factor determines the occurrence of traumatic epilepsy, Russell believes that another factor may explain traumatic epilepsy. He suggests that brain wounds may upset the balance between two antagonistic cerebral mechanisms and that the development of epilepsy may depend upon whether one or the other is the more damaged.

Finally, in studying the social status, it was found that 81% of the patients are earning a living, but that employement is generally unskilled and the mental adjustment to grave disability is often slow and painful. ALPERS, Philadelphia.

CALCIFICATION OF THE CORPUS STRIATUM AND DENTATE NUCLEI OCCURRING IN A FAMILY. J. FOLEY, J. Neurol., Neurosurg. & Psychiat. **14**:253 (Nov.) 1951.

Calcification in the basal ganglia gross enough to be visible roentgenologically occurs in two main groups of conditions: in association with parathyroid insufficiency, and in certain rare familial diseases. Foley reports a case belonging to the latter category in which dense symmetrical calcification in the caudate, lenticular, and dentate nuclei, demonstrable roentgenologically, was associated with intellectual impairment, ataxia, and spasticity. There was no evidence of hypoparathyroidism. Both the patient's daughters, though free of neurological symptoms and signs, exhibited similar, though less well-marked, roentgenological changes. Calcification was not detected in three of the patient's four sons.

The occurrence of hyaline degeneration and gross calicification in these physiologically related nuclei leads to the supposition that their cells have a metabolic peculiarity capable of specific derangement by an elevated level of serum phosphorus or a low level of serum calcium. It is possible that a transient parathyroid insufficiency may cause a permanent, or even progressive, hyaline degeneration in and about the vessels of the basal ganglia.

Foley points out that there is some evidence that the process may result from certain rare chronic infections, and that such infections may affect predisposed families.

In half of the cases reported in the literature symmetrical calicification of the dentate-pallidal system has been associated with hypoparathyroidism, almost always of the idiopathic variety. There is no roentgenological difference between cases with and cases without hypoparathyroidism, though in the latter the calcification tends to be denser.

ALPERS, Philadelphia.

PROLONGED COMPRESSION OF THE BRAIN RESULTING FROM AN EXTRADURAL HEMORRHAGE. G. F. ROWBOTHAM and N. WHALLEY, J. Neurol., Neurosurg. & Psychiat. **15**:64 (Feb.) 1952.

This paper records the unusual sequence of events that occurred in a case of middle meningeal hemorrhage. The clinical developments in the patient, a coal miner of 47, were similar to those of early chronic subdural hemorrhage. Operation was not performed until about a month after the original injury. A large blood clot was encountered in the extradural space. The clot was covered with a thick membrane, such as is seen in chronic subdural hematoma, while the contents consisted largely of dark, watery fluid, such as is found in chronic subdural hematoma, and quite different from the mixture of bright-red blood and gelatinous blood clot seen in acute middle meningeal hemorrhage.

It was believed the signs and symptoms in the first few days after injury were due to bleeding from a posterior branch of the middle meningeal vessels. This bleeding stopped by natural processes, and as the clot began to absorb the patient's mental condition improved. Later, an adventitious membrane began to form around the clot, and possibly an enlarged blood cyst formed, with further compression of the brain. The patient made an uneventful recovery and had no residual disability.

ALPERS, Philadelphia.

ABSCESS FORMATION IN A PITUITARY ADENOMA. N. WHALLEY, J. Neurol., Neurosurg. & Psychiat. **15**:66 (Feb.) 1952.

Whalley describes a patient of 50 who had been in excellent health until two days before admission to the hospital. At that time he complained of headache and began to vomit, and his temperature rose to 103 F. This was followed the next day by the rapid development of complete blindness in both eyes. At this time the clinical picture was that of meningitis. Shortly after losing his vision, he became unconscious and was admitted to the hospital in a semicomatose condition. Shortly after admission he began to have twitchings of all four limbs, which progressed into major epileptic attacks. He died 12 hours after admission. The clinical diagnosis was fulminating meningitis following cavernous sinus thrombosis, presumably secondary to nasal sinus infection.

Autopsy revealed a walnut-sized tumor occupying and protruding upward from the sella turcica, which was widely distended and its posterior wall thinned. The infundibulum of the pituitary gland appeared to be normal. The optic nerves were flattened and stretched over its surface, which showed a purulent exudate. On transverse section the whole left side of the tumor was seen to contain a confluent abscess.

Histologically the appearance of the tumor was that of a simple chromophobe adenoma of the pituitary, with abscess formation, apparently an extension from the left sphenoid air sinus, which contained pus. Cultures of the pus obtained at necropsy showed a growth of Escherichia coli. No organisms were grown from the cerebrospinal fluid.

This patient had undoubtedly had a pituitary adenoma for some time, without evidence of visual disturbance or clinical signs of pituitary dysfunction in the rest of the body. The formation of an abscess within the tumor caused the adenoma to form rapidly and cause rapid compression of both optic nerves. The rapidity of death could be accounted for by spread to the third ventricle, together with pressure on the hypothalamus.

ALPERS, Philadelphia.

DISSEMINATED DEMYELINATING PROCESS OF OVER FIFTY YEARS' DURATION, FIRST SEEN BY DR. WILLIAM OSLER. W. RIESE, G. L. JONES, I. C. EAST, E. BEAMER-MAXWELL, and H. E. DAVIS, Confinia neurol. **12**:8, 1952.

A case of disseminated sclerosis of almost 50 years' duration is described. At autopsy demyelination and gliosis, with relatively good preservation of axis-cylinders, were found in the posterior columns of the spinal cord and in the pons, cerebellum, and cerebral white matter. Accompanying the case presentation is an account of the examination of the patient in 1902 by Dr. William Osler, who made the diagnosis of multiple sclerosis.

FOLEY, Boston.

PONTINE AND BULBOPONTINE TUMORS. J. KAUFMANN, Schweiz. Arch. Neurol. u. Psychiat. **64**:197, 1949.

This study is based on the records of 13 patients with pontine and bulbopontine tumors. The histologic diagnosis was glioblastoma multiforme in five cases, medulloblastoma in 1 case, malignant glioma in 2 cases, astroblastoma in 1 case, astrocytoma in 3 cases, and cavernous hemangioma in 1 case. When the cases were arranged according to the age of the patient at the time of admission, four fell in the first decade of life, two in the second, four in the third, one in the fourth and two in the fifth. Only five patients lived longer than eight months after the appearance of symptoms; three lived one to two years after the onset, and two whose tumors appeared to be situated mainly in the fourth ventricle were still alive, one being able to work eight years after partial removal of the growth.

Localizing signs were classified as follows: (1) cranial nerve paralyses of the peripheral type; (2) cranial nerve paralyses of either the supranuclear or the internuclear type, including nystagmus, paralysis of lateral gaze, and difficulties of articulation and deglutition; (3) disturbances of equilibrium and coordination; (4) involvement of the pyramidal tracts; (5) involvement of the long sensory pathways, and (6) definite evidence of either a bilateral lesion or one producing an alternating paralysis. The author expresses the view that when localizing signs belonging to at least five of the six foregoing groups can be demonstrated it may be concluded that the growth is intrapontine, and hence not amenable to surgical treatment. In 10 of his cases the growth was confined within the substance of either the pons or the pons and medulla oblongata; all six of the above groups of clinical signs were encountered in five of these cases, while five groups of signs were represented in each of the other five cases. On the other hand, in three cases of invasion of the fourth ventricle by a tumor of the pons, the representation was considerably less, although in one of them evidence of an intrapontine growth was more definite one year after partial removal of the tumor. In keeping with the experience of other authors, unequivocal signs of increased intracranial pressure were noted in only five cases, including the three in which the fourth ventricle was invaded.

DANIELS, Denver.

FRONTAL LOBE ABSCESS SECONDARY TO ORBITAL INFECTION AND FACIAL ERYSIPELAS. L. CAMISASCA and L. SALVADORI, Riv. oto-neuro-oftal. **25**:192 (May-June) 1950.

A man aged 26 noted redness of the right cheek, with fever and erysipelas. A few days later exophthalmos and poor vision of the right eye developed. The right frontal sinus was explored, but no pus was found. A few days later fever appeared, with confusion, slow pulse, and headache. Reexploration of the right sinus again failed to reveal pus. Lumbar puncture showed 350 cells per cubic millimeter, with 60% lymphocytes, and 30 mg. of glucose per 100 cc. The left frontal sinus was found to be cloudy and was explored, but no pus was found. Penicillin therapy gave transitory improvement. A few days after the last exploration his condition became worse; the pulse rate fell to 60, and nuchal stiffness developed. The right frontal lobe was punctured and pus was removed. A week after this puncture bilateral papilledema developed, with central scotomas, despite clinical improvement. The choking persisted 15 days and then regressed with no significant diminution of vision. Spread of infection from the face directly to the brain without involvement of the cavernous sinus is rare. The papilledema appearing a week after the incision of the frontal lobe abscess is considered by the authors a toxic reaction, rather than a manifestation of increasing intracranial pressure.

SAVITSKY, New York.

BILATERAL ANOSMIA AS AN EARLY AND SOLE MANIFESTATION OF OLFACTORY-GROOVE MENINGIOMA. L. BARRAQUER-BERRÉ and J. ARUMI FARGAS, Rev. españ. oto-neuro-oftal. **52**:5 (Nov.-Dec.) 1950.

Barraquer-Ferré and Arumi Fargas report the case of a woman aged 45 with a verified olfactory-groove meningioma in whom bilateral anosmia was known to exist as the only symptom for three years. Visual symptoms developed in the fourth year of her disease.

ALPERS, Philadelphia.

INTRACEREBRAL PARACOCCIDIOIDOMYCOSIS GIVING RISE TO A PICTURE OF BRAIN TUMOR. F. H. RITTER, Arq. neuro-psiquiat. **6**:352 (Dec.) 1948.

Maffei reported the first case of intracranial paracoccidioidomycosis in 1943, in which the clinical picture was that of fatal meningitis. Ritter now reports two cases of the condition, one in the cerebrum and the other in the cerebellum. The organism in both cases was identified as Blastomyces (Paracoccidioides) brasiliensis. In both cases a preoperative diagnosis of brain tumor, probably glioma, was made. Nothing in the history or the neurologic examination suggested the presence of a mycotic infection. The spinal fluid in both cases was completely normal. There was no evidence of pleocytosis or increase of protein. The patient with the granuloma in the posterior fossa had an elevated sedimentation rate. One patient lived in the city; the other in the country. Both were men, aged 45 and 48. One of the patients died after the operation. Solitary granulomas must be considered in the differential diagnosis of tumor of the brain in Brazil.

SAVITSKY, New York.

INFERIOR ALTITUDINAL HEMIANOPSIA DUE TO OPTICOCHIASMATIC ARACHNOIDITIS. R. MELARAGNO FILHO, P. BRAGA MAGALHAES, and ROLANDO A. TENUTO, Arq. neuro-psiquiat. **7**:306 (Sept.) 1949.

A white man aged 48 was admitted to the hospital on July 12, 1948. One year before admission he began to complain of diminution of central vision in the left eye. For a short period at the same time he had occipital headaches, radiating to the temple. His headaches were not severe or incapacitating. When they disappeared, his vision became worse. Except for clouding of the right frontal and maxillary sinuses, nothing was found on thorough clinical examination. The spinal fluid showed a pressure of 220 mm. of water but was otherwise normal. The visual disturbances became worse and were noted as especially pronounced in the inferior field. There was no diminution of smell. There was some impairment of sexual potency for six months. The patient was not a drinker or a smoker. Soon after the onset of the present illness operation for sinusitis was done.

On admission to the hospital, his blood pressure was found to be 160/110, and some peripheral arteriosclerosis was noted. There was definite inferior altitudinal hemianopsia. The upper half of each disk was pale, with edema of the lower half. The electroencephalogram revealed no abnormality. The sugar tolerance curve was normal. There were no signs of diencephalic or hypophysial disturbance. Injection of iodized oil into the ventricles showed distortion of the anterior part of the third ventricle and narrowing of the chiasmatic recesses. The diagnosis of opticochiasmatic arachnoiditis was made. A left frontal temple craniotomy, done on August 9, revealed severe and extensive arachnoiditis in the region of the optic nerves and the anterior part of the optic chiasm. No tumor was found on careful examination. Histologic examination of the removed tissue showed nonsyphilitic chronic leptomeningitis.

After the operation there were improvement of visual acuity and slight widening of the visual field. The edema of the inferior part of the disks cleared up. This improvement indicates that the leptomeningeal adhesions played a role in the clinical picture by constricting the optic nerves and chiasm, with some effect on the same area. It was difficult to rule out the existence of lesions in both the optic nerve and the chiasm. The only etiologic factor in this case was sinusitis.

SAVITSKY, New York.

ACOUSTIC NEUROMA REMOVED IN OPERATION, WITH INTACTNESS OF HEARING AND IMPAIRMENT OF VESTIBULAR FUNCTION. C. GAMA, Arq. neuro-psiquiat. **7**:314 (Sept.) 1949.

A white boy aged 15 was admitted to the hospital on Oct. 22, 1947, with a two-year history of frequent vomiting and headaches. He had difficulty with vision and diplopia for one month and was aware of a hearing defect on the left side. Examination showed the following significant signs: left facial paralysis of peripheral type, diminished sensation in the left fifth nerve, paresis of the left side of the palate, bilateral papilledema, more pronounced on the left side, left external rectus paralysis, and horizontal spontaneous nystagmus in either direction, more pronounced to the right. There were a tendency to veer to the left in the Romberg position and dysdiadochokinesia-dysmetria in the left upper limb. The patient's response to the caloric test was impaired on the left.

Special studies showed the initial pressure of spinal fluid to be 230 mm. of water, with a final pressure of 140 mm. after removal of 18 cc. of fluid. The fluid was clear; the Pandy reaction was positive, and the Wassermann reaction was negative. Roentgenograms of the skull showed erosion in the dorsum of the sella, with small suprasellar calcifications, and changes in the petrous process of the left temporal bone. A diagnosis of tumor of the posterior fossa, probably in the left pontocerebellar angle, was made.

Operation was performed on Oct. 28. Removal of a grayish tumor, 3 cm. in diameter, was followed by incision of a cyst containing xanthrochromic fluid. The capsule was also removed. Histologic examination showed it to be a neurinoma. The patient did well after the operation. Nine months later there was no evidence of impairment of cochlear function on the left side. On the other hand, there was absence of response to the caloric test, indicating pronounced involvement of vestibular function on the left side.

SAVITSKY, New York.

CENTRAL NEURINOMA OF THE ACOUSTIC NERVE. P. PINTO PUPO, Arq. neuro-psiquiat. **8**:85 (March) 1950.

A white Brazilian merchant aged 45 was examined on Aug. 17, 1944, complaining of progressive deafness and tinnitus on the left side. After an ailment diagnosed as nephritis from which he suffered toward the end of 1941 he had to rest about a month. After that illness he never felt entirely well. For six months he had complained of tinnitus, diplopia, headache, progressive deafness on the left side, and paralysis of the left side of the face. Neurologic examination showed right-sided pyramidal-tract signs, with right hemiparesis and a right hemisensory syndrome, involving pain, touch, and temperature sensibility, with sparing of the face; impairment of posterior-column modalities on the right side, with ataxia; left facial paralysis of peripheral type; mild diminution of hearing, especially on the left; left external rectus paralysis, and horizontal nystagmus on looking to the right. The patient died suddenly a few days after he was examined. Autopsy showed infarction of the brain stem at the level of the acoustic nerve. A tumor, however, was found in the pons; histologically it looked like a neurinoma. There were no glial elements in the tumor, and an area of softening surrounded it. The diagnosis was neurinoma arising in the intrapontine portion of the acoustic nerve. Signs of pyramidal involvement were present, even though the pyramidal tract was found intact.

SAVITSKY, New York.

NEUROLOGIC COMPLICATIONS OF OSTEOMA OF THE PARANASAL SINUSES: EXTRADURAL PNEUMATOCELE DUE TO OSTEOMA OF THE FRONTAL SINUS; REPORT OF A CASE. R. MELARAGNO FILHO and MOYSÉS CUTIN, Arq. neuro-psiquiat. **9**:133 (June) 1951.

A white man aged 38 entered the hospital with frontal headaches and weakness of the right side of the body of one month's duration. Examination showed mild hemiparesis and deep hyperreflexia on the right side, but no pathologic reflexes; there was no choking of the disk, and examination of the spinal fluid showed a normal status. X-ray examination of the skull revealed a mass in the medial portion of the left frontal sinus and a large collection of gas, evidently extradural, over most of the left cerebral hemisphere. Tomographic studies confirmed the presence of an osteoma and erosion of the posterior wall of the left frontal sinus. An electroencephalogram showed an asymmetrical record, with waves of greater amplitude on the left side. A tumor of the left frontal sinus was removed at operation; the dura was intact.

Histologic study of the tumor showed it to be an osteoma, somewhat eburnated. The hemiparesis was due to pressure of the extradural pneumatocele on the brain. Formation of the pneumatocele in this case was possible because the passage between the frontal sinus and the nose was not occluded by tumor.

SAVITSKY, New York.

POSTENCEPHALITIC PARKINSONISM FOLLOWING INTRAVENOUS HEXOBARBITAL ANESTHESIA. E. JOHN, Wien. klin. Wchnschr. **61**:231 (April 15) 1949.

A woman aged 43 had a history of encephalitis during the epidemic of influenza in 1920, characterized by mild sleep disturbances and lasting only a short time. For all practical purposes, the patient was in good health until 1942, when a right radical mastectomy was performed, with intravenous hexobarbital (evipal) anesthesia. In 1944 a left radical mastectomy was performed, again with the patient under intravenous hexobarbital anesthesia. After this the patient developed typical progressive postencephalitic Parkinsonism. The author believes that the areas originally damaged by the encephalitic process were affected by the drug.

MASON, New York.

Diseases of the Spinal Cord

SENSORY CHANGES WITH HERNIATED NUCLEUS PULPOSUS. L. DAVIS, J. MARTIN, and S. L. GOLDSTEIN, J. Neurosurg. **9**:133 (March) 1952.

Davis, Martin, and Goldstein made a study of the sensory changes in 500 consecutive patients with surgically verified herniated nucleus pulposus. In all but 38 patients myelography was performed and the lesion verified. Of the 500 patients, 327 had demonstrable sensory changes, which were extremely variable. Herniations at the fourth-fifth lumbar interspace alone produced 38 different patterns of sensory involvement, varying from a small area of diminished sensation on the lateral aspect of the calf to hypalgesia of the entire thigh, leg, and foot.

Pinprick and light pin-scratch stimuli were used. It was significant to note the variability of the sensory findings with different examiners. The results also depended to some extent upon the patient's intelligence, suggestibility, and psychical make-up.

The authors found that sensory changes in these 500 patients with herniated nucleus pulposus showed no correlation of the sensory pattern and the level of the lesions. They believe that the extreme variability in the sensory pattern makes the method of devising a dermatome chart from the sensory changes in patients with herniated nucleus pulposus an unreliable one. While myelography is not necessary to establish the diagnosis, they believe it is the most reliable method of localizing the lesion in the lumbar portion of the spine.

ALPERS, Philadelphia.

NEUROMYELITIS OPTICA WITH XANTHOCHROMIA AND SPINAL BLOCK. H. D. MCINTYRE and A. P. MCINTYRE, Neurology **2**:96 (March-April) 1952.

The authors report two cases of neuromyelitis optica complicated by adhesive spinal arachnoiditis, with yellow cerebrospinal fluid and spinal block. In the first case adhesions of the spinal arachnoid and optic chiasm were noted at operation. In the second case it was demonstrated by spinal manometric determinations that demyelination process preceded the adhesive arachnoiditis. An injection demonstrated that the cysts contained polymorphonuclear leucocytes, lymphocytes, macrophages, and red blood cells. In the second case an interval of about 18 months elapsed between the development of optic neuritis and the later appearance of transverse myelitis; 21 days elapsed between the involvements of the right and left eyes.

By presenting illustrative cases, the authors attempt to bring cases of isolated optic neuritis and isolated transverse myelitis into relation with neuromyelitis optica.

The prognosis for the return of serviceable vision is good in neuromyelitis optica. The authors have seen only one surviving patient who remained permanently blind. Remission of both visual and spinal-cord signs may occur, and in this clinical respect the disease resembles multiple sclerosis. The prognosis of the myelitis is more unfavorable than is that of the optic neuritis

because of two possible dangers: (1) that of ascending myelitis, and (2) that of permanent paraplegia, due to compression of the swollen cord by the rigid dura and spine. The over-all mortality rate in the initial attack is at least 50%. Years may elapse between the attack of optic neuritis and the later development of transverse myelitis.

The question of the identity of neuromyelitis optica with acute and remitting multiple sclerosis is still unsettled, with the preponderance of evidence in favor of Hassin's view that neuromyelitis optica is a distinct morbid entity.

The authors feel that those who believe that the acute and remitting forms of multiple sclerosis are identical with neuromyelitis optica must explain the constancy and selectivity of involvement of the optic nerves in conjunction with the transverse lesion of the spinal cord. They must also explain the important fact that surviving patients with neuromyelitis optica do not later show focal demyelination in the brain, brain stem, or spinal cord above the permanent transverse lesion of the cord.

ALPERS, Philadelphia.

HEREDITARY SENSORY RADICULAR NEUROPATHY. D. DENNY-BROWN, J. Neurol., Neurosurg. & Psychiat. **14**:237 (Nov.) 1951.

In 1922 Hicks described a family of 34 members spread over four generations 10 of whom suffered from perforating ulcers of the feet, shooting pains about the body, and deafness. Denny-Brown saw a member of the third generation of this family at the age of 54, during her last illness, and he reports the clinical and necropsy findings.

The postmortem examination disclosed primary degeneration of dorsal root ganglia. Deposits of amyloid were found in the most severely affected ganglia, but they were considered a secondary feature.

In this pedigree the disorder was inherited as a simple Mendelian dominant. The greater loss of sensation of pain and temperature is a result of the radicular pattern of sensory loss. The disease has a sporadic and familial form as well as the hereditary form, and in such cases deafness is absent from the syndrome.

ALPERS, Philadelphia.

NEUROPATHIES CAUSED BY BONY SPURS IN THE CERVICAL SPINE WITH SPECIAL REFERENCE TO SURGICAL TREATMENT. K. L. ALLEN, J. Neurol., Neurosurg. & Psychiat. **15**:20 (Feb.) 1952.

The difficulties and dangers attendant on the surgical approach to the cervical encroachment syndrome have previously prevented full recognition of the deformities responsible for the neurological syndromes found at cervical levels. This paper is based upon operative, roentgenological, and clinical observations and emphasizes the importance of bony spurs as compared with the disk prolapse.

Allen reports a series of 19 operative cases. In these cases cervical osseous spurs, which formed a bridge from side to side anterior to the nerves and cord, were removed. Eight illustrative cases are cited to show the variability of the neurological syndrome encountered and to record the amelioration to be expected from a surgical attack on these abnormalities. All the patients had previously had conservative treatment.

In the author's opinion, prolapsed cervical disk is extremely rare and when present contributes less to the disability than the osseous spur which invariably accompanies it. In all cases reported here the symptoms were attributable to the spur.

Symptoms may be due to root or cord involvement by the spur, separately or in combination. With root involvement pain, with or without neurological signs, is always present. With cord involvement bizarre pictures, with long-tract deficit, arise in the trunk and lower limbs.

Allen prefers the term "spur" to "osteophyte." The spur bridges across anterior to the nerve tissues and should be removed entirely throughout its length. The surgical technique used is described. Posterior laminectomy is considered insufficient.

Surgical treatment should be undertaken only after conservative treatment has failed and when the neurological disability is becoming steadily or rapidly progressive.

ALPERS, Philadelphia.

Treatment, Neurosurgery

NONOBSTRUCTIVE HYDROCEPHALUS: TREATMENT BY ENDOSCOPIC CAUTERIZATION OF THE CHOROID PLEXUS; LONG TERM RESULTS. J. E. SCARFF, J. Neurosurg. **9**:164 (March) 1952.

Scarff reports the results obtained by him in the treatment of nonobstructive hydrocephalus by endoscopic cauterization of the choroid plexus in two series of infants.

In a series of 20 children operated upon prior to 1942, there were 3 hospital deaths, 7 survivals without permanent relief of intracranial pressure, and 10 survivals with permanent relief of pressure. Of the last 10 children, 6 are still living, and 3 of them have average mental development for their ages.

In a series of 19 children operated upon since 1946, there was 1 hospital death, 3 survivals without permanent relief of intracranial pressure, and 15 survivals with permanent relief of pressure. Eleven of these 15 children have average mental development.

Scarff states that the most reliable sign of early hydrocephalus in infants is to be found in the state of the anterior fontanel. He is of the opinion the best criterion known at present for the selection or rejection of cases for surgery is to be found in the thickness of the remaining cerebral cortex, as revealed by ventriculography. He believes that a uniform cortical thickness of 2 cm. will usually assure an average intellectual development, whereas a cortical thickness of less than 1 cm. will preclude it.

ALPERS, Philadelphia.

USE OF BENADRYL® [DIPHENHYDRAMINE] FOR SYMPTOMATIC RELIEF OF "THALAMIC PAIN." R. S. BARRIS, Neurology **2**:59 (Jan.-Feb.) 1952.

Seventeen patients were selected, ranging in age from 46 to 69, in whom the "thalamic syndrome" had been existent for periods of 20 to 1340 days before drug therapy. Oral daily doses of diphenhydramine (benadryl®) hydrochloride, 400 to 600 mg. in divided doses at mealtime and bedtime, were given to each patient. Placebos were introduced after two weeks, at the termination of active diphenhydramine therapy, as a method of establishing control observations. The results of therapy were recorded both objectively, by routine standard testing methods, and subjectively. The observations of attendant personnel were also utilized in evaluating the improvement in the patients' tolerance to various activities.

All patients showed an increased tolerance to otherwise unpleasant stimuli, and the results were described as excellent in 5, good in 10, and fair in 2. Barris believes that diphenhydramine hydrochloride in relatively high doses (400 to 600 mg. daily) is of value in reducing the degree of hyperpathia and spontaneous pain in patients whose signs and symptoms conform to the "thalamic syndrome." In no patient was there complete alleviation of all discomfort associated with hyperpathia, and in three patients the drug in doses of 600 mg. daily produced side-effects consisting of dizziness, sleepiness, or nausea. After temporary discontinuation of the drug, two patients were able to take 400 mg. daily, while with the third its use had to be permanently discontinued.

Little is known as to the pharmacologic site of action of diphenhydramine in ameliorating the discomfort associated with the thalamic syndrome.

ALPERS, Philadelphia.

UNILATERAL PREFRONTAL LOBOTOMY FOR RELIEF OF INTRACTABLE PAIN AND TERMINATION OF NARCOTIC ADDICTION. J. E. SCARFF, Surg., Gynec. & Obst. **89**:385 (Oct.) 1949.

Scarff performed unilateral prefrontal lobotomy for the relief of intractable pain in 33 patients. The follow-up periods ranged from 1 to 10 months. Lobotomy was performed under direct vision, in a plane passing just anterior to the tip of the lateral ventricle, the incision being carried laterally, medially, and ventrally until gray matter was encountered. Results were good in 22 patients, fair in 6, and poor in 5. In 15 patients of this series who had careful psychometric evaluations before and after lobotomy, no significant impairment of intellect or personality could be observed. In 15 of 16 patients heavily addicted to narcotics because of pain prior to operation, abrupt termination of the narcotic dose was effected immediately after operation,

without withdrawal symptoms. An additional patient, appearing to have a primary narcotic addiction, was likewise cured of her dependence on the drug. The results indicate that unilateral prefrontal lobotomy is both an effective and an acceptable measure for the relief of intractable pain in many conditions in which other measures cannot be applied.

J. A. M. A.

RELATION OF STREPTOMYCIN DOSAGE TO NEUROTOXIC SECONDARY EFFECTS. K. GRAF, Schweiz. med. Wchnschr. **79**:793 (Sept. 3) 1949.

According to Graf, the large doses of streptomycin used at first are no longer considered necessary. With lower dosage levels, therapeutically effective, the secondary neurotoxic effects, particularly on the hearing apparatus, are avoided. He studied the relation of dosage levels of streptomycin to secondary neurotoxic effects on 50 adults and 20 children, who received a constant dose of streptomycin by intramuscular injection for at least 30 days. By adaptation of the dose to the body weight of the patient, it was possible to avoid impairment of hearing and disturbances in the vestibular apparatus. In adults the daily dose for intramuscular administration should never be in excess of 24 mg. per kilogram of body weight, because higher doses may produce serious, irreversible vestibular disturbances. A dose of 20 mg. per kilogram (divided into two injections per day), a dose exerting an adequate therapeutic effect, frequently produces vertigo but rarely irreversible disturbances. It is advisable temporarily to interrupt administration of streptomycin if vertigo develops. Secondary effects on the vestibular nerve are much less frequent when the daily dose is 16 mg. per kilogram of body weight. But even with this dosage disturbances are possible when the excretory function of the kidney is impaired. If the renal function is normal, the dose of 16 mg. per kilogram can be continued despite the occurrence of vertigo. Children are less sensitive to the neurotoxic effects of streptomycin, and larger doses can therefore be given them. Severe disturbances in hearing develop only with rather high dosage, especially with intrathecal administration. An intramuscular dose of less than 24 mg. per kilogram causes no disturbances in hearing, provided renal elimination is normal. The high, and to a less extent the low, frequencies are the ones affected in cases in which mild degrees of hardness of hearing result. In the severe degrees all frequencies are uniformly impaired. Mild forms of impaired hearing may subside, but the severe forms do not.

J. A. M. A.

DIPHENYLHYDANTOIN SODIUM IN TREATMENT OF EPILEPSY. F. A. KEHRER, Med. Klin. **44**:1211, 1949.

Kehrer treated patients with idiopathic or residual epilepsy with diphenylhydantoin sodium derivatives. Two preparations, "comital" (0.05 gm. diphenylhydantoin sodium and 0.1 gm. mephobarbital) and "comital L" (0.05 gm. diphenylhydantoin sodium, 0.05 gm. mephobarbital, and 0.05 gm. phenobarbital sodium) were employed. One-half to one tablet was administered three times daily. The number of the attacks was reduced in nearly all patients, or the attacks became less severe. The drugs could be used for ambulatory treatment because of the complete absence of untoward reactions, such as headache, vertigo, vomiting, tremor, or ataxia. Only one patient complained of anorexia and dysphagia, symptoms which may occur in epileptic patients in the absence of any treatment. Many patients remained free from attacks for several months as long as they were taking the drug in the prescribed dose, but attacks recurred when the drug was discontinued or a substitute preparation used. The highly satisfactory results obtained with "comital" are due to the union of diphenylhydantoin sodium with mephobarbital.

J. A. M. A.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

At a meeting of the American Board of Psychiatry and Neurology, Inc., on Oct 11 and 12, 1952, the following two major changes in policy were effected:

1. Applicants who graduated from an approved medical school before the foundation of the Board (1934) will not be held to the strict interpretation of the published requirements in formal graduate training. Under such circumstances the Board will consider the training and experience of the applicant and decide whether or not he will be admitted to the examinations. After Jan. 1, 1954, for such graduates the Board will consider ten years of full-time acceptable experience in psychiatry or neurology in lieu of the formal training requirements. Should the candidate then apply for supplementary certification, the Credentials Committee will require five years of additional acceptable experience in the supplementary field.

2. After July 1, 1954, training credit for work in the field of child psychiatry may be gained only by participation in a hospital residency training program that is regularly approved. After that date, independent training approval of psychiatric clinics for children is discontinued.

The American Board of Psychiatry and Neurology, Inc., announces that the spring examination will be held April 30 and May 1, 1953, at the Langley Porter Clinic, San Francisco. Registration is limited, and early application is advised.

SOCIETY FOR THE ADVANCEMENT OF CRIMINOLOGY

The Society for the Advancement of Criminology will hold a one-day interim meeting, Feb. 24, 1953, at Northwestern University Law School, Chicago. This meeting will immediately precede the 1953 meeting of the American Academy of Forensic Sciences, Feb. 26 to 28, at the Drake Hotel, Chicago. The meeting of the Society for the Advancement of Criminology will be of interest to all those engaged in police-administration education programs on the college level who have not been able to attend the annual meetings in California. The complete program will be announced shortly. All those interested in presenting papers should contact the program chairman, Prof. Ralph F. Turner, Department of Police Administration, Michigan State College, East Lansing, Mich.

HONORARY DEGREE CONFERRED ON DR. THEOPHILE A. ALAJOUANINE

Dr. Theophile A. Alajouanine, professor of clinical neurology and head of the clinic at the University of Paris, France, was granted an honorary degree of Doctor of Science at the University of Illinois Chicago Professional Colleges. The degree was conferred upon him by Pres. George D. Stoddard. Dr. Alajouanine is the first to receive an honorary degree from the University's Chicago Professional Colleges since 1946.

JOINT MEETING OF AMERICAN PSYCHIATRIC ASSOCIATION AND AMERICAN ASSOCIATION FOR ADVANCEMENT OF SCIENCE

The American Psychiatric Association is arranging a program in conjunction with the American Association for the Advancement of Science in St. Louis, on Dec. 29, 1952. The program for the morning and afternoon sessions will consist of a presentation of scientific papers. The evening sessions will be a round-table discussion on "Personality of Scientific Investigators."

GERMAN SOCIETY OF NEUROLOGY

The German Society of Neurology has elected Dr. Percival Bailey honorary member and Drs. W. Penfield, H. Reese, G. Steiner, R. Wartenberg, and F. Wohlwill corresponding members.

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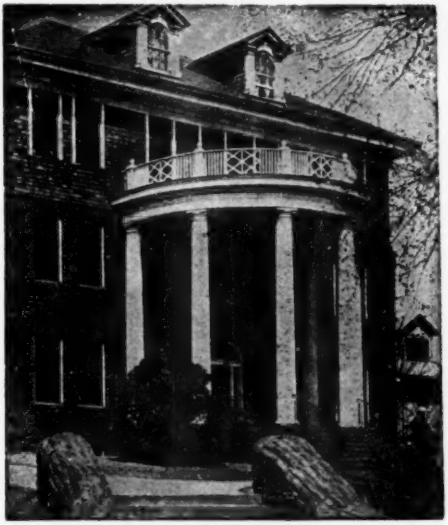

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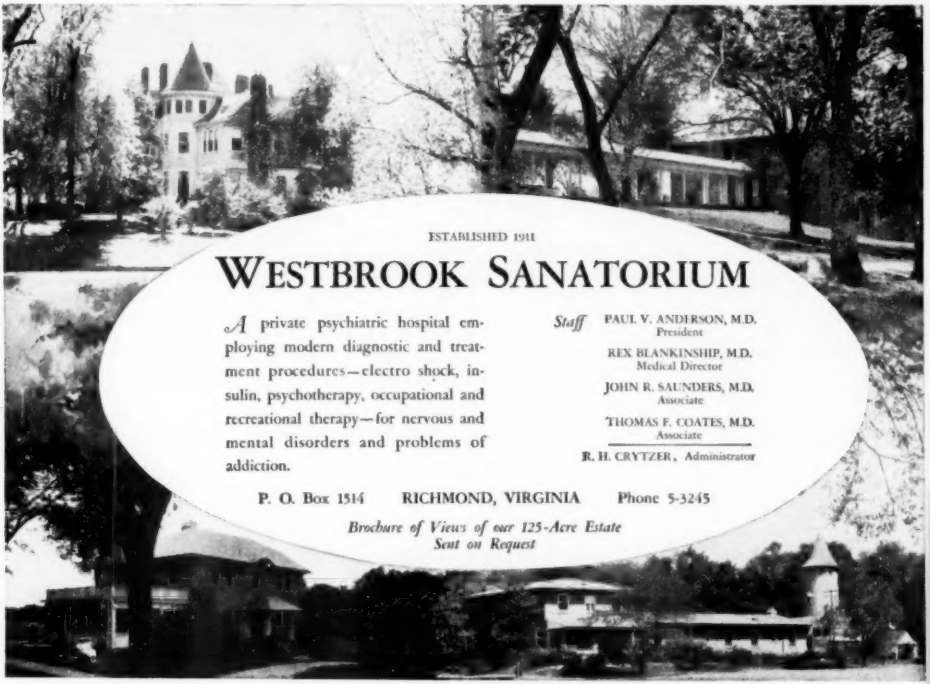

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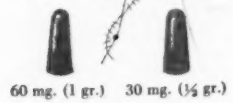

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